A clinical study of association of acute kidney injury and caffeine citrate in preterm neonates

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ABSTRACT

Introduction: Acute kidney injury (AKI) occurs frequently in preterm neonates and is associated with increased morbidity and mortality. **Objective:** The objective of the study was to study the association between caffeine administration and risk of early AKI occurring in the first 7 days after birth and the severity of AKI, defined by modified neonatal Kidney Disease Improving Global Outcomes (KDIGO) staging. **Materials and Methods:** The present study was a retrospective observational cohort of 100 preterm babies admitted in neonatal intensive care unit of a tertiary hospital of South India. All preterm babies with 2 or more serum creatinine (sCr) values were included in this study and neonates with death within 48 h after birth, <1 day of measured urine output on days 2–7 after birth, and fewer than 2 sCr measurements were excluded from the study. Caffeine exposure was determined by review of the inpatient medication record. **Results:** A total of 100 preterm cases were included, out of which 57 cases received caffeine and rest 43 did not. There were 29 cases (29%) who developed AKI in the first 7 days after birth and 9 cases developed Grade 1, 14 cases developed Grade 2, and 6 cases developed Grade 3 AKI according to modified KDIGO guidelines. Neonates who received caffeine were less likely to develop early AKI compared with those who did not (17.5% vs. 44.2%, p=0.004). **Conclusion:** Caffeine administration in preterm neonates is associated with reduced occurrence and severity of AKI. Because of the beneficial effects of caffeine, it may be reasonable to consider its routine use in preterm neonates to prevent or reduce AKI.

Key words: *Acute kidney injury, Caffeine, Serum creatinine*

Acute kidney injury (AKI) is defined as a rapid, potentially reversible deterioration in renal functions sufficient to result in accumulation of nitrogenous wastes in the body (uremia). It is characterized by an increase in serum creatinine (sCr) ≥ 0.3 mg/dl within 48 h or an increase in sCr >/= 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or urine volume <0.5 ml/kg/h for more than 6 h [1].

Assessment of Worldwide AKI Epidemiology in Neonates (AWAKEN) study demonstrated its incidence as 30% in neonates admitted to a neonatal intensive care unit (NICU) and that those with AKI had 4.8 times higher adjusted odds of mortality compared with those without it [2]. Under normal circumstances, the kidneys adapt to various endogenous and exogenous stresses. However, in sick neonates and stressful conditions such as sepsis and shock, the adaptive capacities of the kidney may be overcome leading to renal dysfunction. The incidence of AKI in children appears to be increasing and its etiology has shifted from primary renal disease to multifactorial causes, particularly in hospitalized children. Beyond supportive measures, there are a few specific strategies to prevent AKI, such as avoidance of nephrotoxic drugs and optimization of blood pressure and fluid balance [2,3].

Methylxanthines also known as adenosine antagonists act through A1 and A2A receptors present in the brain, heart, blood vessels, respiratory system, gastrointestinal tract, and kidneys [4]. The three naturally occurring methylated xanthine alkaloids are caffeine, theophylline, and theobromine. To date, the only medication shown to ameliorate AKI in neonates is the adenosine antagonist theophylline [5]. However, because of the narrow therapeutic index, it is no longer used in the general neonatal population [6]. The present study was conducted to find the association between caffeine administration and risk of early AKI occurring in the first 7 days after birth and the severity of AKI, defined by modified neonatal Kidney Disease Improving Global Outcomes (KDIGO) staging.

MATERIALS AND METHODS

The present study is a retrospective observational cohort of 100 preterm babies admitted in the NICU of a tertiary hospital of south India from August 2018 to September 2019. Data were collected from the time of NICU admission until discharge, transfer or death whichever came first. All preterm babies (<37 weeks) with 2 or more sCr values were included in this study. Neonates with death within 48 h after birth or <1 day of measured urine output on days 2–7 after birth or with fewer than 2 sCr values were excluded from the study. Caffeine exposure was determined by

review of the inpatient medication record. Caffeine was used in preterm neonates for various reasons such as to prevent apnea of prematurity, early extubation, and weaning off intermittent positive pressure ventilation.

Both maternal and neonatal data were collected to characterize the cohort and to assess potential confounders, including the maternal age, gestational age, mode of delivery, outborn delivery, pregnancy medications, birth weight, small for gestational age status, sex, resuscitation efforts, ventilation, initial sCr values, and exposure to other neonatal medications, including antimicrobials, diuretics, and vasopressors, in the NICU.

The primary outcome of interest was early AKI occurring in the first 7 days after birth. Neonatal AKI was defined by the modified neonatal KDIGO definition (Table 1) [7]. The secondary outcome was the severity of AKI.

The exposure of interest was administration of caffeine before AKI. If caffeine was used in the first 7 days after birth but after AKI occurred, these neonates were considered not to have received caffeine.

Descriptive and inferential analyses were carried out in our study. Results of continuous measurements were presented in mean±SD and those on categorical measurements were presented in number (%). The Student's t-test was used to find the significance of the study parameters on continuous scale between two groups, intergroup analysis) on metric parameters. Chi-square/Fisher's exact test was used to find the significance on categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Fisher's exact test was used when cell samples were very small. $p<0.05$ was considered statistically significant. The statistical software, namely, SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft Word and Excel were used to generate graphs, tables, etc.

RESULTS

A total of 100 preterm cases were included; out of which, 57 cases received at least one dose of caffeine in the first 7 days after birth and before AKI and rest 43 did not receive caffeine. Neonates who received caffeine were born to mothers who had hypertension, diabetes, cardiac diseases, h/o drug intake, and fever during pregnancy, and h/o obstetric problems. They had lower gestational age and birth weight, were more likely to be resuscitated in the delivery room and on admission, had a diagnosis of respiratory distress and sepsis, and received either invasive or non-invasive respiratory support (Table 2).

Among neonates who developed early AKI, those receiving caffeine had a decrease in Stage 2 or 3. Stage 3 AKI occurred approximately 6 times more frequently among neonates who did not receive caffeine (Tables 3 and 4).

DISCUSSION

AKI is more common in high-risk neonates. Because many preterm and very low birth weight (VLBW) neonates are born before nephrogenesis is complete, incidence of AKI and severity is more common in these neonates. Yet, in spite of the short- and long-term risks of AKI, few specific therapies are available, and none are widely used. This study demonstrates an association between caffeine exposure and AKI. Preterm neonates who were exposed to caffeine were less likely to develop AKI. This association occurred despite the presence of traditional risk factors for AKI among neonates receiving caffeine (including younger gestational age, lower birth weight, and higher illness severity) and persisted even after multivariable adjustment.

There are many studies which demonstrated an association between caffeine exposure and AKI. A single-center retrospective study of VLBW neonates (birth weight <1500 g) by Carmody *et al*. explored that those exposed to caffeine were less likely to experience AKI [8]. Harer *et al*. [9] conducted a secondary analysis of the AWAKEN study. In this multicenter study, among the 675 neonates, included AKI, occurred in 11% of those receiving caffeine compared to 32% of those who did not (adjusted OR 0.20).

The probable mechanism of the action of caffeine-mediated renal protection is after ischemic renal tubular injury, there is an activation of the glomerular adenosine A1 receptor which causes afferent arteriole vasoconstriction, leading to decreased glomerular filtration rate (GFR), salt and water retention, and electrolyte derangements. This may contribute to the morbidity and mortality of patients with AKI [8,10]. Gouyon *et al*. in their study involving newborn rabbits reported that adenosine antagonists counteracted hypoxemia-induced renal hemodynamic changes by maintaining renal vascular resistance [11].

A subsequent study by the same authors demonstrated that theophylline causes increased renal blood flow, enhanced sodium excretion, and a higher GFR [12]. Another possible mechanism is not mediated by any direct association of caffeine with kidney function but is instead conferred through benefits in neonatal respiratory status or hemodynamic stability [13,14]. Using a rodent hyperoxia model, Teng *et al*. demonstrated that caffeine-mediated renal protection may involve attenuation of oxidative stress and injury on endoplasmic reticulum [15]. Further studies are required to know whether any or all of these mechanisms could be relevant in the reduction of AKI as seen in the present study.

Table 1: Definition of acute kidney injury

Stage	sCr	UOP in the past 24 h
0	No change in sCr or rise <0.3 mg/dl	>1 ml/kg/h
1	sCr rise ≥0.3 mg/dl within 48 h or sCr rise between ≥1.5 and 1.9 times reference sCr[a] within 7 d	Between >0.5 and ≤1 ml/kg/h
2	sCr rise between ≥2 and 2.9 times reference sCr	Between >0.3 and ≤0.5 ml/kg/h
3	sCr rise ≥ times reference sCr or sCr≥2.5 mg/dl[b] or receipt of dialysis	≤0.3 ml/kg/h

UOP: Urine output. Reference sCr is the lowest prior sCr value. This value is lower than the original KDIGO definition because an sCr value of 2.5 mg/dl in neonates suggests an estimated glomerular filtration rate <10 ml/min/1.73 m². KDIGO: Kidney Disease Improving Global Outcomes, sCr: Serum creatinine

Table 2: Clinical characteristics of the study population

Variables	Whole cohort (%)	With caffeine (n=57) (%)	Without caffeine (n=43) (%)	p-value
Perinatal factors				
Hypertension	31 (31)	19 (33.3)	12 (27.9)	0.210
Maternal diabetes	8 (8)	6 (10.5)	2 (4.7)	0.460
Cardiac disease	3 (3)	2 (3.5)	1 (2.3)	1.000
Maternal age, mean (SD)	26.97±4.21	27.26±3.67	26.58±4.84	0.425
Primi gravida	42 (42)	23 (40.4)	19 (44.2)	0.700
Multi gravida	58 (58)	34 (59.6)	24 (55.8)	0.700
H/o drug intake	43 (43)	30 (52.6)	13 (30.2)	0.025*
Cesarean delivery	74 (74)	42 (73.7)	32 (74.4)	0.934
H/o fever during pregnancy	11 (11)	8 (14)	3 (7)	0.264
H/o obstetric problems	42 (42)	27 (47.4)	15 (34.9)	0.120
Natal factors				
Gestational age, mean (SD),				
21–28 weeks	9 (9)	7 (12.3)	2 (4.7)	<0.001**
28–34 weeks	23 (23)	18 (31.6)	5 (11.6)	
34–37 weeks	68 (68)	32 (56.1)	36 (83.7)	
Birth weight, mean (SD), g	1.71±0.49	1.59±0.44	1.87±0.52	0.005**
SGA status, no. (%)	44 (44)	26 (45.6)	18 (41.9)	0.839
Male, no. (%)	55 (55)	36 (63.2)	19 (44.2)	0.059
Resuscitation required	32 (32)	20 (35.1)	13 (30.2)	0.446
AKI risk factors				
Perinatal asphyxia	13 (13.0)	6 (10.5)	7 (16.3)	0.397
RDS	48 (48)	33 (57.9)	15 (34.9)	0.023*
Mechanical ventilation	66 (66)	43 (75.4)	23 (53.5)	0.022*
Sepsis/probable sepsis	53 (53)	43 (75.4)	10 (23.2)	<0.001**
NEC	11 (11)	5 (8.8)	6 (14)	0.523
Nephrotoxic drugs	56 (56)	38 (66.7)	18 (41.8)	0.013*
Shock	18 (18)	11 (19.3)	7 (16.3)	0.697
Dehydration fever	8 (8)	0	8 (18.6)	0.001**
Babies undergoing any surgery	1 (1)	0 (0)	1 (2.3)	0.430

Neonates who received caffeine were less likely to develop early AKI compared with those who did not (p=0.004). AKI: Acute kidney injury

Table 3: Association of caffeine administration with AKI within 7 days

AKI	With caffeine (n=57) (%)	Without caffeine (n=43) (%)	Total (n=100) (%)	p-value	OR (95% CI)
No	47 (82.5)	24 (55.8)	71 (71.0)	0.004**	0.27 (0.11–0.67)
Yes	10 (17.5)	19 (44.2)	29 (29.0)		

AKI: Acute kidney injury

Table 4: Association of caffeine administration with secondary AKI outcomes

Stage of AKI	With caffeine	Without caffeine	Total	p-value
Stage 1	4 (7.1)	5 (11.6)	9 (9.0)	0.020
Stage 2	5 (8.8)	9 (20.9)	14 (14.0)	
Stage 3	1 (1.8)	5 (11.6)	6 (6.0)	

AKI: Acute kidney injury

The study had a few limitations. The participants were not randomized to receive caffeine. Second, a dose-dependent effect of caffeine could not be evaluated. Third, our clinical laboratory uses an alkaline picrate (Jaffe) method for the measurement of sCr. This methodology may overestimate its value. As KDIGO scale defines AKI based on percentage change in sCr, this may have led to an underestimation of AKI.

CONCLUSION

Caffeine administration in preterm neonates is associated with reduced occurrence and severity of AKI. Due to the benefits and favorable adverse effective profile of caffeine, it may be reasonable to consider routine use of prophylactic caffeine in preterm neonates to prevent or reduce AKI, even when apnea of prematurity or the need for positive pressure respiratory support is absent.

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