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A Study of the Association between Early Caffeine Citrate Administration and Risk of Acute Kidney Injury in Preterm Neonates

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ABSTRACT

Background: Commonly in newborns, acute kidney injury (AKI) to be linked to poor clinical outcomes, which in turn is linked to higher rates of morbidity and mortality. Caffeine administration may save low-birth-weight newborns from acute renal injury.

Objectives: This study aimed to explore the relationship between caffeine citrate administration and AKI in preterm neonates in the first 7 days after delivery, and to test the hypothesis that caffeine administration would be linked with lower frequency and severity of AKI.

Methods: This study included 68 preterm neonates of both sexes from the NICU of Menoufia University who were divided into 2 groups. Group I comprised (34) preterm neonates who received caffeine citrate. Group II comprised (34) preterm neonates who did not receive caffeine citrate.

Results: There was no statistically significant difference in urea and creatinine levels among the studied groups in the first while there was a statistical difference in the third and seventh days as those who received caffeine citrate showed lower values than those who did not receive caffeine citrate. There was a statistically significant difference between the two groups in AKI staging as the majority (82.4%) of cases in group I was stage 0 while near to half (58.8%) of cases in group two were stage 1. There was no statistically significant difference between the two groups as regards consanguinity and delivery, while there was statistically significant difference between group I and group II as regards gestational age, weight and Apgar score 1 and 5 (P =0.001).

Conclusion: Giving caffeine to premature neonates was linked to a lower incidence of AKI.

Keywords: Neonates, AKI, Caffeine citrate.

INTRODUCTION

Physicians are focusing more and more on minimizing the premature short-term and long-term repercussions as the survival rate of preterm neonates has increased [1]. Significant findings and developments in the last five to ten years have improved our understanding of neonatal AKI and our ability to care for neonates with renal dysfunction. The neonatal kidney collaborative has played an important role in this development. The capacity to care for babies who can benefit from extracorporeal treatments has increased as new therapies have been developed [2].

AKI is common in the NICU and has been associated to increased morbidity and mortality rates. Furthermore, infant AKI may increase the risk of developing CKD. The definition of newborn AKI has evolved and grown more standardized as a consequence of ongoing research, making it simpler to evaluate and describe the epidemiology and outcomes associated with neonatal AKI [2, 3].

AKI in newborns can be caused on by many factors. The low GFR, which increases 8-fold during the first week and continues to rise until the age of two months, the lower renal blood share of cardiac output, which returns to normal levels by the age of two and the reduced medullary tonicity, which causes hypotonic urine. Poor tubular function causes the first positive potassium balance essential for the preterm neonate's development. Later, there is an accelerated diuresis that, if it does not happen, may result in AKI [4]. AKI is difficult to diagnose in the early postnatal days because of growing renal physiology and imprecise diuresis measurements. For a cohort of newborns born between 2008 and 2018, a screening procedure for AKI can be tailored using the clinical profile of a patient cohort, and this profile can also form the basis of a renal follow-up program in the NICU [5].

AKI is known to independently correlate with higher morbidity and mortality rates, yet effective treatments remain limited. Current evidence from randomized clinical trials indicates that theophylline, an adenosine antagonist, is the medication shown to mitigate AKI in neonates [6].

Adenosine antagonists include methylxanthines, which act on A1 and A2 receptors in the brain, heart, blood vessels, respiratory system, gastrointestinal tract, and kidneys. Methylxanthines may prevent AKI or improve renal function in high-risk neonates and babies, such as those suffering from prenatal hypoxia/ischemia, being born prematurely, or after heart surgery. These findings originate from clinical studies that used theophylline or aminophylline [3, 7]. However, these drugs are no longer commonly utilized in the newborn population. A research discovered that caffeine citrate (another methylxanthine) accounted for 96% of methylxanthine consumption [5].

According to **Aithal and Kandasamy** [7], a retrospective single center study of newborns with exceptionally low birth weights (birth weight < 1500 g) may help prevent acute renal impairment at an early stage of caffeine administration. Therefore, the

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purpose of this study was to explore the hypothesis that caffeine administration would be linked to a lower incidence and severity of AKI and to investigate the relationship between caffeine citrate administration and AKI in preterm neonates during the first seven days after delivery.

PATIENTS AND METHODS

This cohort study included 68 preterm neonates of both sexes from NICU of Menoufia University who were divided into 2 groups; Group I comprised 34 preterm neonates who received caffeine citrate and group II comprised 34 preterm neonates who did not receive caffeine citrate. The study fulfilled inclusion and exclusion criteria after obtaining consents from ethical committee and the responsible authorities with consents from parents.

Inclusion criteria: Pre-term and near-term neonates (gestational age from 29 weeks to 36 weeks) attending the early administration of caffeine citrate and its effect on renal function and participants in this study who received intravenous fluids for at least the first 48 hours after admission.

Exclusion criteria: Neonates with known systemic illness (renal, liver and cardiac disease), preterm neonates with multiple congenital anomalies and preterm neonates of high risk factors e.g. of pregnant mothers highly exposed to radiation.

Methods of data collection: Routine medical history through complete detailed medical history (prenatal, natal and postnatal) and routine clinical assessment by thorough clinical examination was assessed. Additionally, renal function assessment via regular labs and follow up during the duration of staying at the NICU and regular follow up via laboratory investigation was done. Complete blood count (CBC) was performed by 2 ml of blood on EDTA tube by Advia 2120 apparatus, which use laser light scatter technology for determination of blood count and platelet count. Arterial blood gases (ABG), PH, CO_2 percentage and O_2 saturation in blood were measured. Serum electrolytes (Na^+, K^+, Ca^{++}) were estimated using the indirect ion-sensing (ISE) approach employing auto-analyzers (AA) placed in hospitals' central labs. Renal function tests (Urea & creatinine analysis) were tested in blood or urine. Using a tiny needle, a medical practitioner extracted blood from an arm vein. A tiny volume of blood was drawn into a test tube or vial following the needle's insertion.

Ethical approval: The Ethics Committee of Menoufia Faculty of Medicine approved this investigation. Each participant completed a permission form when all information was received. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis

Version 20.0 of the IBM SPSS software program was used to examine the data that was supplied into the computer. The distribution's normality was confirmed using the Kolmogorov-Smirnov test. The mean ± standard deviation, and range (minimum and maximum) were used to characterize quantitative data. Percentage and numbers were used to describe the qualitative data. The following tests were performed to determine the significance of the results at the 5% level: For qualitative data, the Chi-square test was employed, while the Student t-test was employed to compare the means of the quantitative data.

RESULTS

The current study found that 32.4% were males among group I while 52.9% were males among group II with no statistically significant difference. There was no statistically significant difference between the two groups as regards consanguinity as group I and group II showed only 5.9% and 8.8% consanguinity respectively. Most of the neonates were delivered by Cesarean section (91.2% & 88.2% among group I and group II respectively) (Table1). Gestational age and weight showed significant difference in favor of group II without caffeine.

Table (1): Demographic data among the studied cases

	Caffeine citrate administration (n = 34)		No Caffeine citrate administration (n = 34)		Test of sig.	P. value
	No.	**%**	**No.**	**%**		
Gander					X^2 = 2.94	0.08
Male	11	32.4%	18	52.9%		
Female	23	67.6%	16	47.1%		
Consanguinity						
Yes	2	5.9%	3	8.8%	X^2 = 0.28	0.64
No	32	94.1%	31	91.2%		
Delivery					X^2 = 0.15	0.69
Normal vaginal delivery	3	8.8%	4	11.8%		
Cesarean section	31	91.2%	30	88.2%		
Gestational age (weak)					t –test =4.03	0.001*
Min.–Max	29.0 – 35.0		30.0 – 36.0			
Mean ± SD.	32.23± 1.87		34.34 ± 1.72			
Weight (kg)					t -test =4.92	0.001*
Min.–Max	0.9 – 2.9		1.1 – 2.9			
Mean ± SD.	1.56± 0.38		1.97 ± 0.39			

χ2: Chi-square test, t: independent sample Student's t-test, *: Statistically significant at P ≤ 0.05

There was no statistically significant difference about all vital signs. There was statistically significant difference between the two groups in Apgar Score 1 and 5 among the studied groups as the score were high in group II who did not receive caffeine citrate. It also showed that there was statistically significant difference between the two groups in SPO_2 (p value =0.05) as the mean value in group I was 96.0% and it was 95.55% in group II. While there was no statistical difference in other arterial blood gases. There was no statistically significant difference in regard to serum electrolytes among the studied groups. There was statistically significant difference as regards random blood glucose (RBG) among the studied groups (Table 2).

Table (2): Vital signs and lab investigation among the studied groups

Vital signs & lab investigation	Caffeine citrate administration (n = 34)	No Caffeine citrate administration (n = 34)	t-test (p-value)
	Mean ±SD	**Mean ±SD**	
SBP (mmHg)	80.47±12.36	81.6± 11.25	**0.18 (0.81)**
DBP (mmHg)	40.95±10.21	45.25 ±10.11	**1.85 (0.07)**
Heart rate (beat/min)	141.12 ± 11.32	141.32 ±9.06	**0.08 (0.91)**
Temperature (ºC)	36.83± 0.37	36.74 ± 0.42	**0.4 (0.85)**
Respiratory rate (N/min)	54.63 ± 6.34	53.53 ± 7.39	**0.65 (0.51)**
APGAR 1	4.18 ± 1.46	4.18 ± 1.46	**9.14 (0.001)***
APGAR 5	5.21 ± 1.78	5.21 ± 1.78	**8.34 (0.001)***
PH	7.21 ± 0.07	7.32 ± 0.04	**0.54 (0.51)**
SPO_2 (%)	**96.05**± 1.07	95.55 ± 1.02	**2.27 (0.03)***
PCO_2 (%)	33.37 ± 9.10	34.42 ± 8.55	**0.47 (0.61)**
HCO_3 (mmol/L)	17.78 ± 3.30	19.16 ± 2.92	**1.67 (0.07)**
Na^+ (mEq/L)	139.47 ± 5.6	139.68 ±6.2	0.14 (0.87)
K^+ (mEq/L)	4.55 ± 0.83	4.31 ± 0.69	1.67 (0.27)
Ca^{++} (mg/dL)	1.50 ± 0.34	1.13 ± 0.16	0.90(0.36)
RBS (mg/dL)	205.18 ± 15.13	84.03 ± 17.50	**3.28 (0.04)***
CRP (mg/L)	12.46 ± 2.86	27.56 ± 6.4	**2.44 (0.78)**

t: independent sample Student's t-test, *: Statistically significant at P ≤ 0.05

The finding showed that there was no statistically significant difference in urea level among the studied groups in the first day while there was statistical difference in third and seventh days as those who received caffeine citrate showed lower values than those who did not receive caffeine citrate**.** There was no statistically significant difference in creatinine levels among the studied groups in the first day while there was statistical difference on third and seventh days as those who received caffeine citrate showed lower values than those who did not receive caffeine citrate (Table 3).

Table (3): Blood urea level and serum Creatinine level among the studied groups

		Caffeine citrate administration (n = 34)	No Caffeine citrate administration (n = 34)	t test (p value)
		Mean ± SD.	Mean ± SD.	
Urea (mg/dl)	**First day**	35.48 ± 8.75	35.48 ± 8.75	**1.84 (0.07)**
	Third day	28.55 ± 7.08	28.55 ± 7.08	**2.36 (0.028)***
	Seventh day	33.61 ± 8.38	33.61 ± 8.38	**3.43 (0.031)***
Creatinine (mg/dl)	**First day**	1.86± 0.41	1.86± 0.41	**0.94 (0.35)**
	Third day	1.62 ± 0.22	1.62 ± 0.22	**2.19 (0.018)***
	Seventh day	0.73 ± 0.17	0.73 ± 0.17	**0.43 (0.031)***

t: independent sample Student's t test, *: Statistically significant at P ≤ 0.05.

Table (4) showed that there was no statistically significant difference between the two groups as regards the outcome and most cases were discharged or survived but only one case (2.9%) died in group I and 4 cases (11.76%) in group II. there was statistically significant difference between the two groups as regards hospital stay as the mean value of hospital stay was 16.36 in group I while it was 26.97 in group II. There was statistically significant difference between the two groups as regards hospital stay as the mean value of hospital stay was 16.36 in group I while it was 26.97 in group II.

Table (4): Diagnosis and outcome among the studied cases

	Caffeine citrate administration (n = 34)		No Caffeine citrate administration (n = 34)		Test of sig.	P. value
	No.	**%**	**No.**	**%**		
Diagnosis					X^2 **= 9.78**	**0.20**
Congenital pneumonia	2	5.9%	0	0.0%		
Hyaline membrane disease	8	23.5%	4	11.8%		
N. J	0	0.0%	2	5.9%		
Respiratory distress syndrome	20	58.8%	17	50.0%		
Sepsis	0	0.0%	1	2.9%		
Transient tachypnea newborn	4	11.8%	9	26.5%		
Outcome						
Died	1	2.9%	4	11.76%	X^2 **= 3.85**	**0.29**
Discharged	14	41.2%	8	23.5%		
Survived	19	55.9%	22	64.7%		
Hospital stay (days)						
Mean ± SD.	16.36± 6.88		26.97 ± 6.39		**t -test =5.98**	**0.001***

χ2: Chi-square test, t: independent sample Student's t-test, *: Statistically significant at P ≤ 0.05.

Table (5) found that there was statistically significant difference between the two groups in AKI staging as the majority (82.4%) of cases in group I was stage 0 while near half (58.8%) of cases in group two were stage 1.

Table (5): AKI among the studied groups

AKI	Caffeine citrate administration (n = 34)		No Caffeine citrate administration (n = 34)		Test of sig.	P. value
	No.	**%**	**No.**	**%**		
Stage 0	28	82.4%	9	26.4%	X^2 **= 24.14**	**0.001***
Stage 1	4	11.8%	20	58.8%		
Stage 2	2	5.9%	5	14.7%		

χ2: Chi square test, *: Statistically significant at P ≤ 0.05,
Stage 0: no significant changes in creatinine
Stage 1: increase in Scr by 0.3mg/dl within 48h or increase in Scr by 150% to 200% from previous trough
Stage 2: increase in Scr by 200% to 300% from previous trough
Stage 3: increase in Scr by 300% from previous trough or increase in Scr by 2.5mg/dl orRRT

DISCUSSION

Caffeine treatment in premature newborns was linked to a lower incidence and severity of AKI, according to a newly published study. Preterm newborn death rates have been considerably lowered by recent improvements in neonatal care [1, 2].

The current study found that there was no statistically significant difference between the two groups in terms of consanguinity or delivery, however there was a significant difference between groups I and II in terms of gestational age and weight (P = 0.001). The study by **Al Hamshary *et al.*** [8] also discovered that group I (with caffeine) had substantially shorter gestational age and birth weight than group II (p-value = 0.000). This is consistent with prior research by **Sivasaranappa and Aara** [9] who found that neonates with a lower gestational age and birth weight were more likely to receive caffeine. **Harer *et al.*** [10] found similar findings when they gave caffeine to newborns with earlier gestational ages and lower birth weights. These consistent results from many research highlight the link between caffeine intake and neonatal features such as reduced gestational age and birth weight.

In terms of gestational age (GA), the current findings contradicted those of **Carmody *et al.*** [11], who found no statistically significant change in GA, birth weight, or sex distribution between neonates given caffeine and those not given caffeine. Also, **Mansour *et al.*** [12] showed that there was no statistically significant difference in GA or birth weight between the two groups. The differences in results might be explained by the varying sample sizes in each research and the different criteria for newborns according to the nation.

The findings of the current study also indicated that caffeine citrate did not significantly impact the levels of sodium, potassium, or calcium. This suggests that caffeine citrate administration does not require additional interventions or monitoring specifically for these electrolytes. However, standard electrolyte monitoring remains important in clinical practice to ensure overall metabolic balance and health. The lack of significant differences in serum electrolytes supports the safety profile of caffeine citrate in terms of electrolyte balance [13].

The present investigation revealed that there was statistical significant difference as regards random blood glucose (RBG) among the studied groups. Caffeine's impact on glucose metabolism is less well understood. It is possible that caffeine citrate may influence glucose metabolism either directly or indirectly, through metabolic or endocrine pathways. For instance, caffeine can influence insulin sensitivity and glucose metabolism, potentially leading to higher glucose levels. Caffeine citrate could affect the stress response in neonates or patients, which might lead to increased glucose production and release from the liver [14]. Given the significant difference in RBG levels, it is essential to monitor blood glucose levels closely in patients receiving caffeine citrate [15]. On the first day, there was no significant difference in urea levels and creatinine levels between the two groups. This indicates that the initial impact of caffeine citrate on urea levels might not be apparent immediately after administration. Both groups had similar baseline urea levels and creatinine, suggesting that any effects of caffeine citrate on renal function or urea metabolism may not be detectable in the very early stages of treatment [16-17].

The significantly lower mean urea level in the caffeine citrate group (33.61 mg/dL) compared to the non-caffeine citrate group (71.85 mg/dL) suggests that caffeine citrate administration is associated with better renal function or lower urea production at this time point [18]. The trend continues on the seventh day, with the caffeine citrate group maintaining lower urea levels (27.79 mg/dL) compared to the non-caffeine citrate group (45.56 mg/dL). The sustained difference suggests a longer-term impact of caffeine citrate on renal function or urea metabolism [19]. The significant differences in urea levels observed on the third and seventh days highlight a potential benefit of caffeine citrate in improving renal function or affecting urea metabolism. While, the absence of significant differences on the first day suggests a delayed effect, the sustained lower urea levels in the caffeine citrate group indicates that this treatment may contribute to better renal outcomes over time [20-22]. The statistically significant lower creatinine levels in the caffeine citrate group compared to the non-caffeine citrate group indicates that caffeine citrate may influence renal function positively over a few days.

The sustained lower creatinine levels in the caffeine citrate group on the seventh day reinforce the notion that caffeine citrate might have a longer-term beneficial effect on renal function. **Mohamed *et al.*** [21] found that on the second day following admission, the average urea and creatinine levels in the patients under study were 27.49 ± 16.90 mg/dL and 0.82 ± 0.27 mg/dL, respectively. On the seventh day following admission, the mean creatinine was 0.53 ± 0.19 mg/dL and the mean urea was 15.39 ± 7.48 mg/dL. Preterm newborns have much lower renal flow, which raises the risk that they may present with AKI due to renal ischemia. It should be underlined that, from an anatomical and physiological perspective, renal immaturity makes life outside of the womb challenging. This is often made worse by pharmacological nephrotoxicity, malnourishment, and other issues that arise when a patient is in the hospital [5, 10, 15].

As regards creatinine, **Mansour *et al.*** [12] on day three reported no statistically significant change in creatinine between the two groups under study (P=0.674), however on days five and seven, there was a statistically significant difference. Serum creatinine

level was higher in the group that didn't receive caffeine at day 5 and day 7 as compared to the group who received caffeine. This is consistent with the findings of **Aviles-Otero *et al.*** [13] who demonstrated that patients who received caffeine and those who did not had identical baseline blood creatinine levels. The percentage change in baseline serum creatinine (62% vs. 105%; p=0.003) and peak serum creatinine (median 1.0 mg/dl vs. 1.5 mg/dl; p=0.008) were lower in caffeine-treated individuals than in non-caffeine-treated ones. Our findings are consistent with **Carmody *et al.*** [11] who demonstrated that caffeine consumption did affect peak blood creatinine levels in the first ten days following delivery.

The Apgar score is a quick assessment tool used to evaluate the health of newborns immediately after birth. Scores are given at 1 minute and 5 minutes post-delivery, with higher scores indicating better overall neonatal health and stability [19]. The finding of lower Apgar scores in the caffeine citrate group at both 1 and 5 minutes suggests that the administration of caffeine citrate may be associated with less favorable early neonatal outcomes. This could be due to several factors as caffeine citrate is primarily used to stimulate the respiratory drive in preterm infants. While, it is effective in improving respiratory function over time, its immediate impact on other aspects of neonatal health may not be as pronounced [11]. These results corroborated those of **Sivasaranappa and Aara** [9] who found that whereas neonates who were not given caffeine had higher Apgar scores after five minutes, there was a statistically significant difference between the groups at one minute. **Al Hamshary *et al.*** [8], on the other hand, found no statistically significant difference in Apgar scores between group I and group II ranging from 1 to 5 minutes.

As regards length of hospital stay and mortality, the current study showed that there was no statistically significant difference between the two groups as regards the outcome, the majority of cases were discharged or survived but only one case (2.9%) died in group I and 4 cases (11.76%) in group II. In study by **Mansour *et al.*** [12], they reported that both length of stay and mortality were higher in the group of neonates that didn't receive caffeine (group B) but the difference didn't reach a statistically significant value [12]. Similar findings were reported by **Carmody *et al.*** [11], who found that the group of newborns who did not receive caffeine had a greater incidence of death and a longer length of hospital stay, but the difference was not statistically significant. Numerous investigations, including those by **Srinivasan *et al.*** [5], **Harer *et al.*** [10] **and Jetton *et al.*** [22] have resurrected the subject of neonatal AKI. The findings of their study showed that AKI in critically sick newborns is prevalent and reliably linked to negative outcomes.

The current study revealed a statistically significant difference in AKI staging between the two groups, with the majority (82.4%) of patients in group I being stage 0, whereas almost half (58.8%) of cases in group two were stage one. These findings are similar to the results of **Sivasaranappa and Aara** [9] who reported that neonates who consumed caffeine were less likely to have early AKI than those who did not (17.5% vs 44.2%), p=0.004). Caffeine therapy in premature neonates has been associated to a lower incidence and severity of acute kidney injury. Caffeine's beneficial properties make frequent use in preterm babies a reasonable option for avoiding or reducing AKI. This is also consistent with **Carmody *et al.*** [11] who reported on a single-center retrospective study of very low birth weight (VLBW) neonates (birth weight less than 1500) to see if caffeine consumption was associated with a lower risk of AKI.

In the greatest research of the relationship between caffeine and newborn AKI, **Harer *et al.*** [10] did a secondary analysis of 675 neonates from the AWAKEN trial. Their study focused on neonates delivered before 33 weeks gestational age and sought to investigate the relationship between caffeine administration and acute kidney injury within the first 7 days of life. Researchers found that neonates who consumed caffeine during this period had a considerably reduced incidence of AKI compared to those who did not (11.2% vs. 31.6%, $p < 0.01$) [10]. Several putative pathways for caffeine and other methylxanthines to decrease AKI have been hypothesized. **Gouyon and Guignard** [23] found that neonatal rabbits treated by coffee or theophylline had increased renal blood flow, salt excretion, and GFR. They also showed that theophylline reduced hypoxemia-induced renal hemodynamic alterations by maintaining renal vascular resistance. Another proposed mechanism for caffeine's renal protective effects is the reduction of oxidative stress and the mitigation of endoplasmic reticulum damage. Also, it was found that theophylline improves renal blood flow, salt excretion, and GFR [24]. Another probable mechanism is that caffeine confers improvements in infant respiratory status or hemodynamic stability, rather than directly affecting kidney function [13, 14]. A meta-analysis of randomized controlled trials found that theophylline reduced contrast-induced AKIs in the general population, in addition to the good results in babies [25]. These contradictory data suggest that the therapeutic efficacy of adenosine antagonism is dependent not only on the medicine but also on the patient group and the etiology of AKI. The link between caffeine and AKI may not be due to kidney confusion or intrinsic activity, but rather to caffeine's beneficial non-renal effects [26].

CONCLUSION

The current study showed that administering caffeine to preterm infants is linked with a decreased risk and severity of AKI. There was statistical difference in third and seventh days as those who received caffeine citrate showed lower values than those who did not receive caffeine citrate. There was statistically significant difference between the two

groups as regards hospital stay where group I showed shorter hospital stay than group II (without caffeine).

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