Association between Caffeine Citrate and Incidence of Acute Kidney Injury in Preterms

Abstract

Background: As a result of prematurity, Acute kidney injury (AKI) occurs commonly in preterm neonates and is associated with increased morbidity and mortality. (AKI) is defined as a rapid, potentially reversible deterioration in renal functions sufficient to result in accumulation of nitrogenous wastes in the body. **Aim of the study** the aim of this study was to determine whether preterm neonates who took caffeine citrate from the first day after birth were less likely to AKI within the first 7 days. **Patients and Methods:** This case control study was conducted on 100 preterm neonates at Neonatal Intensive Care Units (NICUS), Pediatric Department, Tanta University with gestational age less than (30 weeks) were grouped into group A and B. **Group A** 50 preterm neonates who received caffeine citrate from the first day after birth with dose (20 mg/kg) loading dose, and (5 mg/kg/dose) every 24hrs of maintenance dose, given as slow intravenous infusion over twenty to thirty minutes for a week. **Group B** 50 preterm neonates who did not receive caffeine citrate.

A- Hematological Investigations: serum albumin, serum creatinine, blood urea**.**

B- Urinary Investigations: measuring urine output.

Results: There was a statistically significant difference between the two studied groups as regard serum creatinine in day (5,7) ($p<0.001$), urea in day 7 (p value <0.001), serum albumin in day (5,7) (p value ≤ 0.05), urine output in day (4,5,6,7) (p value ≤ 0.05), AKI incidence (p value <0.001). **Conclusion:** Caffeine Citrate administration in preterm neonates from the first day of life for one week was associated with reduced occurrence and severity of AKI.

Keywords: Caffeine Citrate, Incidence, Acute Kidney Injury, Preterms.

1. Introduction:

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].

Many etiological factors predispose development of AKI in preterms, these factors include a low Apgar score, sepsis, hypothermia, nephrotoxic drugs, various therapeutic interventions (catheterization, intubation, mechanical ventilation, etc.), dehydration, haemodynamically significant patent ductus arteriosus (PDA) and severe intracranial hemorrhage [2,3].

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 [4,5]

Caffeine citrate (another methylxanthines) is presently one of the most prescribed medicines in neonatal units. It is the first choice among all methylxanthines because of its efficacy, better tolerability and wider therapeutic index as well as longer half-life [6].

In clinical trials neonates who received caffeine had greater urine output compared with those who did not, as caffeine induces diuresis by enhancing renal blood flow as well as glomerular filtration rate. It also increases creatinine clearance and urinary calcium excretion; however, it does not induce any changes in serum sodium, potassium**.** This is primarily mediated via its adenosine antagonistic activity in the kidneys [7].

1.1 Aim of the study the aim of this study was to determine whether preterm neonates who took caffeine citrate from the first day after birth were less likely to AKI within the first 7 days.

2. Patients and Methods:

This case control study was carried out at Neonatal Intensive Care Units (NICUs), Pediatric Department, Tanta University Hospital on 100 preterm neonates with gestational age less than 30 weeks divided into two groups**; Group A**: Included 50 preterm neonates who received caffeine citrate from the 1st day after birth on the safety dose. **Group B**: included 50 preterm neonates who didn't receive caffeine citrate. The neonates within **group A** were given **caffeine citrate** from the 1st day of life for one week with dose (20 mg/kg) loading dose, and (5 mg/kg/dose) every 24 hours of maintenance dose, given as slow intravenous infusion over twenty to thirty minutes.

2.1 Inclusion criteria: all preterms <30 weeks admitted within first 24 hours after birth presented by respiratory distress according to Downes' score **(Wood DW et al, 1972)[8]**

2.2 Exclusion criteria:

- Newborns with congenital heart disease except non-significant PDA.
- Neonatal mortality < 48 h of life.
- Clinical signs suggest chromosomal anomalies.
- Newborns with congenital renal anomalies.

2.3 Methods:

All newborns included in the study were subjected to the following after an informed consent from their parent and approval from the Ethical Committee of Tanta University Hospital:

- Full history for every involved case will be taken including prenatal, antenatal, postnatal and maternal history (diseases and medications).
- All cases in the study will be clinically examined for:
  - General conditions such as activity, skin color any obvious congenital abnormalities or syndromatic features.
  - Vital signs (respiratory rate, heart rate, temperature and blood pressure).
  - Anthropometric measures (weight, head circumference, abdominal circumference and height), sex, delivery mode, Apgar score in the first and fifth minute, and gestational age using New Ballard score.
- Hematological Investigations:
  - Serum Creatinine level was measured on (the third day of life). After that, the serum creatinine values were analyzed (every other day) for the first 7 days.
  - Serum Urea and Albumin were measured on the (third day of life).after that, they were measured (every other day) for the first 7 days.
- Urinary investigations:
  - Urine output was measured by daily urine collection for one week provided by measuring the weight of diapers. (calculation of corrected diaper weight every 3 hours). Normal daily UOP should be ≥ 1 ml/kg/h.

2.4 Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**) (Kirkpatrick and Feeney, 2013)**

3. Results:

- There was no statistically significant difference within the two groups as regard gender, mode of delivery, age, weight, length, head circumference, APGAR1 and APGAR 2, respiratory rate, heart rate, MAP, serum creatinine in day 3, urea in day 3 and 5, serum albumin in day 3, UOP in the first, second and third day, noninvasive and invasive ventilation, medication exposure, length of stay and mortality.
- There was a statistically significant difference between the two studied groups according to serum creatinine, observed in day 5 and day 7 ($p<0.001$).
- There was a statistically significant difference between the two studied groups according to blood urea observed in day 7 (p value <0.001)
- There was a statistically significant difference between the two studied groups according to serum albumin, observed in day 5 and 7 (p value ≤ 0.05).
- There was a statistically significant difference between the two studied groups according to urine output observed in day 4, 5, 6 and 7 (p value ≤0.05).
- There was a statistically significant difference between the two studied groups according to AKI (p value <0.001).

Table 1: Comparison between the two studied groups according to demographic data and anthropometric measures

	Group A (n = 50)		**Group B (n = 50)**		**Test of Sig.**	**P**
	No.	**%**	**No.**	**%**		
Gender						
Male	23	46.0	27	54.0	χ^2= 0.640	0.424
Female	27	54.0	23	46.0		
Mode of delivery						
Vaginal	21	42.0	16	32.0	χ^2= 1.073	0.300
Cesarean	29	58.0	34	68.0		
Age (week)						
Min. – Max.	26.0 – 30.0		26.0 – 30.0		t= 0.054	0.976
Mean ± SD.	28.54 ± 0.93		28.54 ± 0.99			

Median (IQR)	29.0 (28.0 – 29.0)	29.0 (28.0 – 29.0)		
Weight (gm)				
Min. – Max.	750.0 – 1450.0	750.0 – 1450.0	t= 0.031	0.976
Mean ± SD.	1134.0 ± 155.3	1133.0 ± 171.3		
Median (IQR)	1150.0(1050.0– 1250.0)	1175.0(1000.0– 1250.0)		
Length (cm)				
Min. – Max.	35.50 – 42.0	35.60 – 41.20	t= 0.945	0.347
Mean ± SD.	38.34 ± 1.42	38.60 ± 1.26		
Median (IQR)	38.70 (37.20 – 39.0)	38.40 (38.0 – 39.20)		
H.C (cm)				
Min. – Max.	23.40 – 27.50	23.20 – 27.90	t= 0.144	0.886
Mean ± SD.	26.07 ± 0.92	26.05 ± 1.03		
Median (IQR)	26.40 (25.50 – 26.60)	26.35 (25.50 – 26.60)		

χ^2: Chi square test, t: Student t-test, p: p value for comparing between the studied groups, IQR: interquartile range

Table 2: Comparison between the two studied groups according to APGAR 1&2

	Group A (n = 50)	**Group B (n = 50)**	**T**	**P**
APGAR 1(1^{st} min)				
Min. – Max.	3.0 – 6.0	3.0 – 7.0	1.566	0.121
Mean ± SD.	4.56 ± 0.88	4.26 ± 1.03		
Median (IQR)	5.0 (4.0 – 5.0)	4.0 (3.0 – 5.0)		
APGAR 2(5^{th} min)				
Min. – Max.	6.0 – 9.0	5.0 – 9.0	0.628	0.531
Mean ± SD.	7.62 ± 0.88	7.74 ± 1.03		
Median (IQR)	8.0 (7.0 – 8.0)	8.0 (7.0 – 8.0)		

t: Student t-test, p: p value for comparing between the studied groups, APGAR: Apgar score

Table (3): Comparison between the two studied groups according to vital signs

Vital signs	Group A (n = 50)	Group B (n = 50)	T	P
Respiratory (rate/min)				
Min. – Max.	39.0 – 58.0	40.0 – 60.0		
Mean ± SD.	49.20 ± 5.05	49.86 ± 4.43	0.695	0.489
Median (IQR)	49.0 (46.0 – 53.0)	50.0 (47.0 – 53.0)		
Heart (rate/min)				
Min. – Max.	106.0 – 183.0	104.0 – 186.0		
Mean ± SD.	146.4 ± 22.79	148.2 ± 24.04	0.389	0.698
Median (IQR)	144.5 (127.0 – 165.0)	152.5 (128.0 – 168.0)		
MAP				
Min. – Max.	36.0 – 75.0	35.0 – 76.0		
Mean ± SD.	55.88 ± 7.90	55.68 ± 8.66	0.121	0.904
Median (IQR)	56.50 (51.0 – 61.0)	57.0 (50.0 – 62.0)		

t: Student t-test

p: p value for comparing between the studied groups

Table (4): Comparison between the two studied groups according to serum creatinine

s.Creatinine (mg/dl)	Group A (n = 50)	Group B (n = 50)	U	P
Day 3				
Min. – Max.	0.41 – 1.0	0.42 – 0.92		
Mean ± SD.	0.66 ± 0.16	0.67 ± 0.14	1189.0	0.674
Median (IQR)	0.67 (0.53 – 0.80)	0.65 (0.55 – 0.80)		
Day 5				
Min. – Max.	0.24 – 1.0	0.47 – 1.27		
Mean ± SD.	0.67 ± 0.25	0.87 ± 0.18	745.0*	<0.001*
Median (IQR)	0.71 (0.44 – 0.90)	0.88 (0.74 – 0.95)		
Day 7				
Min. – Max.	0.10 – 1.80	0.79 – 2.25		
Mean ± SD.	0.78 ± 0.49	1.20 ± 0.30	605.50*	<0.001*
Median (IQR)	0.83 (0.35 – 1.14)	1.13 (0.97 – 1.34)		

U: Mann Whitney test

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

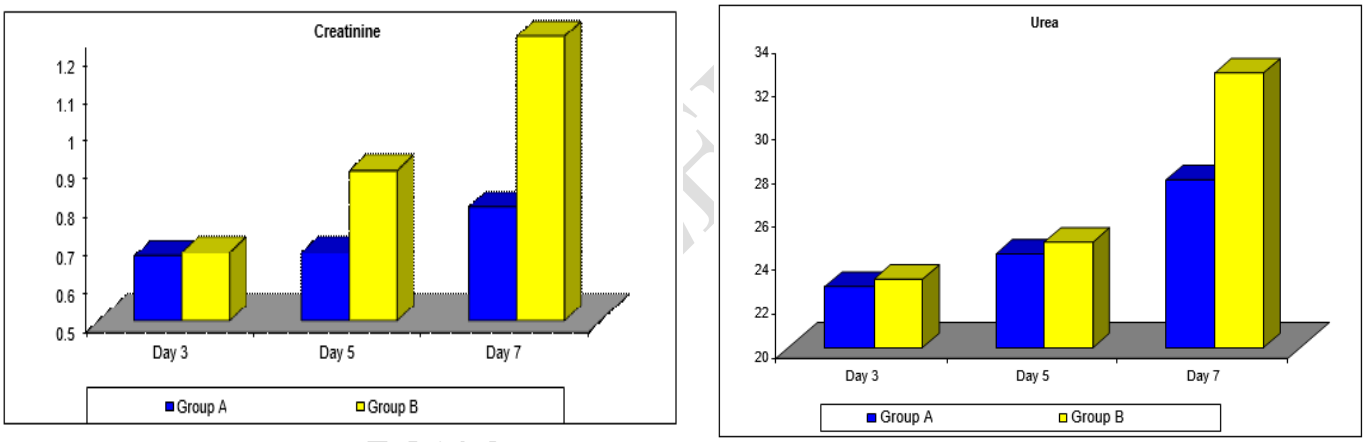
Table (5): Comparison between the two studied groups according to urea

Urea (mg/dl)	Group A (n = 50)	Group B (n = 50)	T	P
Day 3				
Min. – Max.	5.20 – 35.10	17.80 – 30.20		
Mean ± SD.	22.79 ± 4.23	23.13 ± 2.48	0.482	0.631
Median (IQR)	22.55 (21.0 – 24.10)	23.20 (21.70 – 24.90)		
Day 5				
Min. – Max.	16.50 – 36.40	17.40 – 35.10		
Mean ± SD.	24.31 ± 5.70	24.84 ± 4.41	0.524	0.602
Median (IQR)	23.10 (20.20 – 29.10)	24.05 (21.90 – 27.0)		
Day 7				
Min. – Max.	17.80 – 46.70	20.10 – 42.30		
Mean ± SD.	27.71 ± 6.95	32.65 ± 4.89	4.108*	<0.001*
Median (IQR)	26.35 (23.0 – 30.90)	32.95 (28.50 – 36.50)		

t: Student t-test

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$



(A) (B)

Figure 1: Comparison between the two studied groups according to (A) serum Creatinine and (B) urea.[

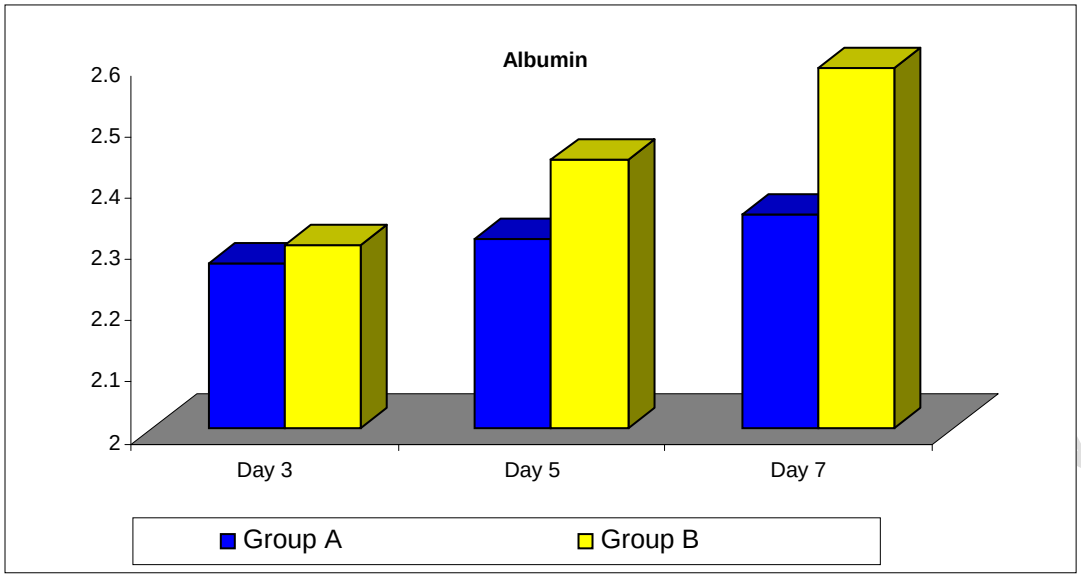


Figure 2: Comparison between the two studied groups according to serum Albumin.

Table (6): Comparison between the two studied groups according to UOP

UOP (ml/kg/h)	Group A (n = 50)	Group B (n = 50)	U	P
Day 1				
Min. – Max.	18.0 – 50.0	11.0 – 50.0		
Mean ± SD.	29.51 ± 7.13	28.24 ± 7.62	1130.500	0.410
Median (IQR)	30.0 (24.0 – 34.0)	27.0 (21.90 – 34.0)		
Day 2				
Min. – Max.	16.0 – 54.0	17.0 – 53.0		
Mean ± SD.	32.37 ± 8.52	30.80 ± 7.70	1094.500	0.283
Median (IQR)	34.50 (26.0 – 38.0)	29.50 (24.0 – 36.0)		
Day 3				
Min. – Max.	15.0 – 54.0	19.0 – 54.0		
Mean ± SD.	33.82 ± 9.85	32.73 ± 7.36	1064.500	0.201
Median (IQR)	36.0 (30.0 – 42.0)	31.60 (27.0 – 38.0)		
Day 4				
Min. – Max.	13.0 – 56.0	17.0 – 51.0		
Mean ± SD.	34.07 ± 11.13	31.25 ± 6.59	936.500*	0.031*
Median (IQR)	35.0 (27.0 – 43.0)	30.55(26.50 – 36.0)		
Day 5				
Min. – Max.	11.0 – 61.0	15.0 – 45.0	925.500*	0.025*
Mean ± SD.	33.78 ± 12.42	30.07 ± 6.83		

Median (IQR)	36.0 (27.0 – 43.0)	30.0 (26.70 – 34.0)		
Day 6				
Min. – Max.	1.30 – 60.0	11.0 – 47.0		
Mean ± SD.	33.04 ± 13.87	28.83 ± 7.60	907.0*	0.018*
Median (IQR)	33.0 (27.0 – 43.0)	29.05 (24.0 – 34.0)		
Day 7				
Min. – Max.	7.40 – 62.0	12.0 – 48.0		
Mean ± SD.	33.46 ± 14.71	28.34 ± 8.77	932.500*	0.029*
Median (IQR)	33.0 (24.0 – 45.0)	29.65 (22.0 – 35.0)		

U: Mann Whitney test
p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

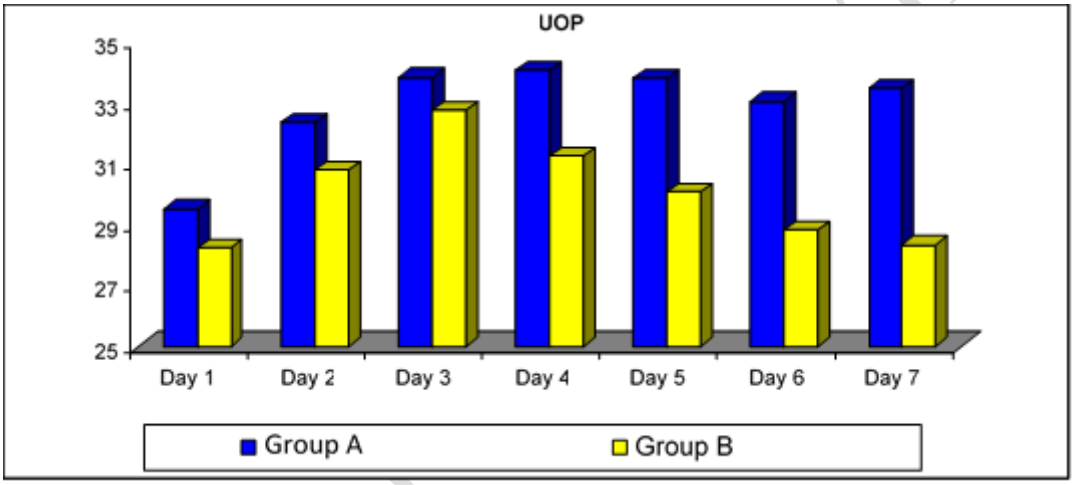


Figure 3: Comparison between the two studied groups according to UOP

Table 7: Comparison between the two studied groups according to incidence of AKI and ventilation

AKI	Group A (n = 50)		Group B (n = 50)		χ^2	P
	No.	%	No.	%		
No	40	80.0	23	46.0	**12.398***	**<0.001***
Yes	10	20.0	27	54.0		
ventilation						
Invasive ventilation	25	50.0	26	52.0	0.040	0.841
Non-invasive ventilation	41	82.0	38	76.0	0.542	0.461

χ^2: Chi square test, p: p value for comparing between the studied groups, *: Statistically significant at $p \leq 0.05$

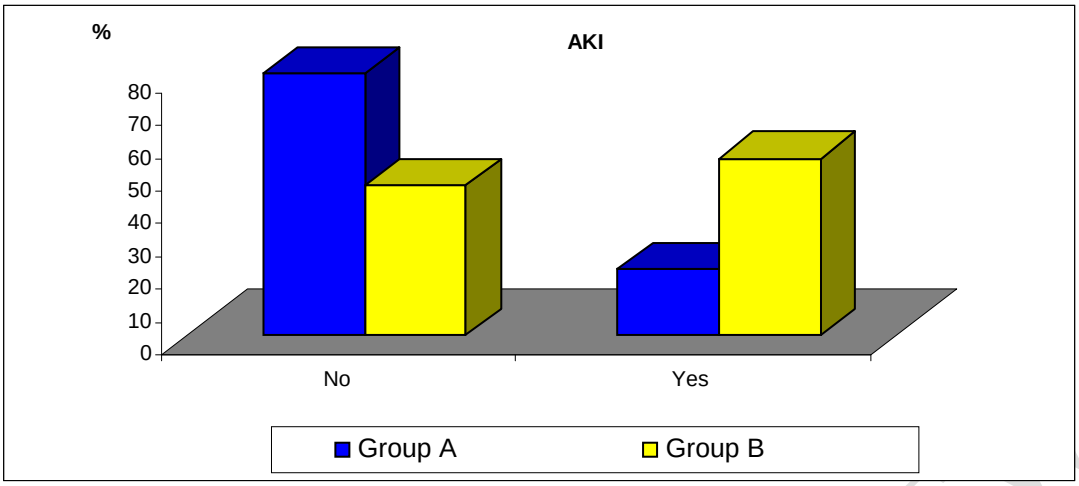


Figure (4): Comparison between the two studied groups according to incidence of AKI

Table 8: Comparison between the two studied groups according to medication used

	Group A (n = 50)		Group B (n = 50)		χ^2	P
	No.	%	No.	%		
AMIKIN	43	86.0	38	76.0	1.624	0.202
Dopamine	12	24.0	11	22.0	0.056	0.812
Lasix	10	20.0	7	14.0	0.638	0.424
Surfactant	12	24.0	10	20.0	0.233	0.629

χ^2: Chi square test, p: p value for comparing between the studied groups

Table 9: Comparison between the two studied groups according to length of stay and mortality

Length of stay (days)	Group A (n = 50)	Group B (n = 50)	U	P
Min. – Max.	16.0 – 73.0	19.0 – 86.0	1046.0	0.159
Mean ± SD.	45.62 ± 17.99	51.12 ± 20.16		
Median (IQR)	47.50 (32.0 – 60.0)	51.50 (32.0 – 68.0)		
Mortality				
No	49	98.0	2.837	0.204
Yes	1	2.0		

χ^2: Chi square test, FE: Fisher Exact, U: Mann Whitney test, p: p value for comparing between the studied groups

Table 10: Odds ratio

	AKI				COR	95% CI		AOR	95% CI	
	No		Yes							
	No.	%	No.	%		LL	UL		LL	UL
Exposure to Caffeine	40	63.5	10	27.0	0.213*	0.088	0.518	0.049*	0.011	0.211

COR: Crude Odds ratio, AOR: Adjust Odds ratio by gender, age, weight, invasive ventilation, amikacin, dopamine and lasix.

Exposure to caffeine is a protective agent against development of AKI. The Crude Odds ratio for development of AKI after exposure to caffeine is 0.213. The Adjust Odds ratio is 0.049 indicating more decrease in the incidence of AKI after exposure to caffeine after adjustment of by gender, age, weight, invasive ventilation, amikacin, dopamine and Lasix.

4. Discussion

In the current study, there were 23 males (46.0%) and 27 females (54.0%) in the caffeine group (group A) while there were 27 males (54.0%) and 23 females (46.0%) in the no caffeine group (group B) with no statistically significant difference in the sex distribution within the two groups (p=0.424). there was no statistically significant difference between the two groups in mean GA or in the mean birth weight.

As regard gestational age; the current results agreed with Carmody et al. who showed that there was no statistically significant difference in the GA, birth weight and sex distribution between the neonates who received and didn't receive caffeine [9].

The difference between the results could be explained due to different sample size in each study and different criteria of the neonates according to the country.

As regard Apgar score; in the current study, there is no statistically significant difference observed between the two studied groups as regards APGAR 1 and APGAR 2, where p value equals 0.121 and 0.531 consequently.

As regard Apgar; our results were in disagreement with Harer and his colleagues as they reported that neonates who did not receive caffeine had greater Apgar scores at 5 minutes [10].

The difference between the two studies is due to the selection criteria and our results are considered to be more accurate as it avoided the selection bias that could affect the accuracy of the results.

As regard creatinine; in the current study, there is no statistically significant difference observed between the two studied groups as regards creatinine in day 3 (P=0.674) while there is a statistically significant difference observed between the two studied groups in day 5 and day 7 (p<0.001). Serum creatinine level was higher in the group that didn't receive caffeine (0.87 ± 0.18 mg/dl and 1.20 ± 0.30 mg/dl) at day 5 and day 7 as compared with the group who received caffeine (0.67 ± 0.25 mg/dl and 0.78 ± 0.49mg/dl). This came in accordance with Aviles-Otero who showed that there was no difference in baseline serum creatinine between patients who did and did not receive caffeine. However, patients who received caffeine had lower peak serum creatinine (median 1.0 mg/dl vs. 1.5 mg/dl; p=0.008) and percentage change in baseline serum creatinine (62% vs. 105%; p=0.003) than those who did not. Similarly, patients receiving caffeine had a lower absolute change from baseline serum creatinine than those who did not receive caffeine [11].

Our results also agreed with Carmody et al. who showed that peak serum creatinine during the first 10 days after birth did vary by caffeine exposure. The median age at peak serum creatinine was 4 days (IQR 2-6) and did not vary by receipt of caffeine (P = 0.74, Mann-Whitney U). Initial creatinine did not differ by caffeine exposure (caffeine: 0.65 mg/dl; no caffeine: 0.69 mg/dl; P = 0.36) [9]. **As regard AKI;** in the current study, the incidence of AKI in group A who received caffeine was 20% which was significantly lower as compared with group B who didn't receive caffeine (54%). The cases who developed AKI in group A

were all at stage 1, while the cases who developed AKI there in group B were (96.3%) at stage 1, (3.7%) at stage 2, there was lower number AKI from group A (10 cases) than those of group B (27 case) from total cases (50 in each group), so there is statistically significant difference observed between the two studied groups, p value <0.001. Also, our study showed that exposure to caffeine is a protective agent against development of AKI. The Crude Odds ratio for development of AKI after exposure to caffeine is 0.213. The Adjust Odds ratio is 0.049 indicating more decrease in the incidence of AKI after exposure to caffeine after adjustment of by gender, age, weight, ventilation, medication used. **As regard AKI;** our results were also in agreement with Sivasaranappa and Anjum Aara who showed that the incidence of AKI in group of neonates who received caffeine was 17.5% which was significantly lower as compared with the group of neonates who didn't receive caffeine (44.2%). The cases who developed AKI in group were (7.1%) stage 1, (8.8%) stage 2 and (1.8%) stage 3 while in cases who didn't receive caffeine there were (11.6%) stage 1, (20.9%) stage 2 and (11.6%) stage 3[12].

There are several potential mechanisms of action through which caffeine and possibly other methylxanthines could directly reduce AKI. In investigations involving newborn rabbits exposed to caffeine or theophylline, Gouyon and Guignard reported increased renal blood flow, enhanced sodium excretion, and a higher glomerular filtration rate [13].

A subsequent study by the same authors demonstrated that methylxanthines counteracted hypoxemia-induced renal hemodynamic changes by maintaining renal vascular resistance [14]..

These discrepant results suggest that not only the drug, but also the patient population and mechanism of AKI are relevant in determining the clinical utility of adenosine antagonism. In this study, we did not attempt to identify the cause of AKI and could not determine a differential effect among the likely multiple etiologies of AKI in our population.

Another potential mechanism of caffeine-mediated renal protection may involve attenuation of oxidative stress and injury on endoplasmic reticulum [15].

As regard ventilation; in the current study, there was no statistically significant difference between the two groups in the incidence of use non-invasive ventilation and invasive ventilation. Also, there was no statistically significant difference in the incidence of use of different drugs including Amkin, Dopamine, Lasix and Surfactant. Similar results were reported by Carmody and his colleagues **[9]**.

As regard length of stay and mortality; in the current study, by comparing the two studied groups according to length of stay and incidence of mortality in both groups, both were higher in the group of neonates that didn't receive caffeine (group B) but the difference didn't reach a statistically significant value. Similar results were reported by Carmody et al. who sowed longer length of hospital stay and higher incidence of mortality in the group of neonates that didn't receive caffeine but the difference didn't reach a statistically significant value **[9].**

Unfortunately, our study has some limitations including that it is single center study, the relatively small sample size, limited time of the study and limited follow up duration.

We were unable to evaluate a dose-dependent effect, therapeutic targets because medication dosages and systemic levels of caffeine citrate were not collected in the study, therefore we could only assess short-term associations of caffeine citrate administration with kidney function.

5. Conclusion:

Caffeine Citrate administration in preterm neonates from the first day of life for one week was associated with reduced occurrence and severity of AKI.

6. Recommendation:

Using Caffeine Citrate from the 1st day of life for one week with dose (20 mg/kg) loading dose, and (5 mg/kg/dose) every 24 h of maintenance dose, given as slow intravenous infusion for twenty to thirty minutes reduced occurrence and severity of AKI in preterm neonates.

CONSENT AND ETHICAL APPROVAL

All Newborns in this study were subjected to the following after an informed consent from their parent and approval from the Ethical Committee of Tanta University Hospital: History taking, carful clinical examination, specific investigational studies.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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