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# Preventive Value Of Caffeine Citrate Against The Risk Of Acute Kidney Injury In Preterm Neonates

**A.H.S.Al Hamshary[1], O.S.El Shaaier[2], D.R.Soliman[1], M.B.E.Hassanin[3] and E.A.I.Haggag[3]**
[1]Pediatric, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[2]Clinical and chemical pathology, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[3]Neonatology, Dept., Faculty of Medicine, Al Galaa teaching hospital –GOTHI
E-mail:dr.emanhaggag@gmail.com

**Abstract**

Background: In preterm newborns, acute kidney damage (AKI) often develops. Administration of caffeine may prevent acute renal damage in extremely low neonates of birth weight. The objective of this research was to determine if administering caffeine citrate to premature infants will alter the occurrences of AKI. Methods: This case-control research was conducted on preterm neonates hospitalised to Benha University and Algalaa Teaching Hospital in neonatal critical care centres. All neonates were divided into two groups: Group I: included (50) premature newborns receiving citrate of caffeine. Group II: comprised (50) non-caffeine citrate preterm newborns. The definition of the modified newborn kidney disease (KDIGO) has been utilised for the evaluation of acute kidney injury stage. Result: 45 percent of all preliminary newborns admitted to our neonatal intensive care unit (NICU) had AKI in this research. The AKI rate among exposed groups of caffeine was 38 percent, statistically significantly lower than AKI among exposed groups of non-caffeine (52 percent). Wert P = 0.015. Statistically significantly shorter gestational age and birth weight were in Group I than Group II There was no statistically significant difference in delivery method, sex, apgar scores for 1 and 5 minutes between group I and group II. Conclusions: Caffeine is linked with decreased risk of acute renal damage in preterm babies.

**Key words:** Neonates, Caffeine citrate, AKI.

## 1. Introduction

As survival rate of preterm neonates has Improved physicians concentrate more and more on reducing the premature short-term and long-term consequences [1].

There have been considerable progress over recent years in our abstract knowledge of acute kidney injury (AKI) and its effects on medical outcomes [2].

In premature newborns, acute kidney damage (AKI) is common and is linked with increased morbidity and mortality [3].

Prerenal failure owing to renal hypo-perfusion or ischemia is the most frequent type of (AKI) in newborns. Pre-renal failure may lead to kidney failure if not treated quickly. Because of its physiological characteristics such as a high renal vascular resistance, high plasma renin activity, low glomerular filters, lower intracortical perfusion rate and decreased sodium re-absorption in the proximal tubes in the first few days of neonate the neonate kidneys are most susceptible to hypo-perfusion. Newborn children are thus susceptible to acute tubular necrosis or cortical necrosis. In neonates, the cause (AKI) is multi-factorial aetiology and there are typically one or more contributing variables. Peri-natal asphyxia and sepsis are the most frequently related disorders in most research. Other related problems for neonatal development (AKI) include respiratory stress syndrome, dehydration, heart failure and nephrotoxic medications [4].

A multicenter (24 sites in 4 countries) research on the incidents, risk factors and results of newborn AKI was started in 2014 by the Neonatal Kidney Collaborative (NKC) and named the Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) project. The research showed that 30 percent of neonates hospitalised to a newborn intensive AKI unit with AKI had an adjusted death rate 4.8 times greater than neonates without AKI. But there are few particular methods for preventing or improving AKI outside support measures, such as nephronic toxins prevention and blood pressure optimization and fluid balance. Identification of treatments to prevent or decrease the severity of AKI is thus crucial [5].

Methyl xanthines are antagonists of adenosines that operate via A1 and A2A receptors in the brain, heart, blood vessel, respiratory system, gastrointestinal tract and kidneys. Caffeine citrate is a methyl xanthine, which is used as a first line therapy for apnea premature, or as a second line therapy for apnea that has not responded to theophylline or for the prevention of apnea preterm babies; [6].

Carmody et al. [7] indicated that a retrospective single centre research of extremely low birth weight neonates (birth weight < 1500 g) may help avoid an acute renal damage early on administration of caffeine. [7].

The objective of this research was to determine if the administration of caffeine citrate to preterm infants would alter the incidence of AKI.

## 2. Patients and Methods

This research was conducted out on premature newborns hospitalised to the Benha University Hospital and Algalaa Teaching Hospital's neonatal critical care departments over the period September 2019 to April 2020. Following the permission of the Ethical Research Committee of the faculty of

Medicine, Benha University, the research was conducted and parental consents were informed in writing from all individuals participating in the study.

The preterm neonates of both genders with gestational age below 37 weeks of admission to NICU and received intravenous fluids were included in this research for at least the first 48 hours following admission. Premature neonates hospitalised 14 days and more after delivery to NICU were excluded from the research, premature neonates with severe congenital defects and with mortal chromosome abnormalities and with maternal history of renal impairment. All neonates were divided into two groups: Group I comprised (50) newborns who have received caffeine citrate and Group II (50) neonates that have not received caffeine citrate.

All two groups were the following

Maternal and neonatal history: age of mothers, method of delivery, pregnancy, estimated gestational age, birth weight, sex, resuscitation, admission diagnosis, ventilation, patent ductus arteriosus therapy, exposure to coffeine and other newborn medicines.

Conditions and edoema if available

Examination of the central nervous system: (fontanllae, tone, conscious level, reflexes, and seizures). Examination of the respiratory system: (air entry, grunting, intercostal retractions, apnea, tachypnea and cyanosis). Cardinal system: (heart rate, perfusion, blood pressure). Gastrointestinal: ( feeding tolerance, abdominal distension, vomiting).

Routine lab tests (CBC, CRP, Urea and BUN) were performed on day 3.

The serum creatinine laboratory test was researched; at the 3rd, 5th and 7th days three serial samples were drowned. Baseline serum creatinine was measured using this table at day 3 of age.

The collected data were tabulated and analyzed using SPSS version 24 software (Spss Inc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test ($X^2$), or Fisher's exact test (FET) were used to analyze categorical variables. Quantitative data were tested for normality using Kolomogrov Smirnove test assuming normality at P>0.05. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was used to analyze normally distributed variables among 2 independent groups, or Man Whitney U test for nonparametric ones. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant)

## 3. Results

All participating neonates were classified into two groups: Group I included (50) preterm neonates (44% male and 56% female) which received caffeine citrate in the first 7 days after birth and Group II included (50) preterm neonates (40% male and 60% female) not receiving caffeine citrate.

- This table shows that, Gestational Age was statistically significant lower among Group I than Group II (p value= 0.000) and birth Weight was statistically significant lower among

Group I than Group II (p value= 0.000). There were no statistically significant difference between group I and group II regarding Mode of Delivery, sex, Resuscitation Effort, Apgar 1m and Apgar 5 Table (3).

- This table shows that, there were no statistically significant difference between group I and group II regarding admission diagnosis Table (4).
- The percentage of AKI among Group I was 38% which was statistically significant lower than AKI among Group II (52%). P value= 0.015 Table (5).
- Regarding KIDGO classification of AKI, mean value of staging of AKI at Day 7 was statistically lower in Group I than Group II ,P value= .001 Table (6).

**Table (1)** Normal serum creatinine values of term and pre-term infants [8]

| Age(day) | <28wk | 28-32wk | 32-37wk | >37wk |
|---|---|---|---|---|
| **3** | 1.05 ± 0.27 | 0.88 ±0.25 | 0.78 ± 0.22 | **0.75 ± 0.2** |
| **7** | 0.95 ± 0.36 | 0.94 ± 0.37 | 0.77 ± 0.48 | 0.58 ± 0.4 |
| **14** | 0.81 ± 0.26 | 0.72 ± 0.36 | 0.62 ± 0.40 | 0.43 ± 0.25 |
| **28** | 0.66 ± 0.28 | 0.59 ± 0.38 | 0.40 ± 0.28 | 0.34 0.2 |

The modified neonatal Kidney Disease Improving Global Outcomes (KDIGO) definition was used for assessment of the stage of acute kidney injury based on serum creatinine results

**Table (2)** The modified neonatal Kidney Disease Improving Global Outcomes (KDIGO) definition

| AKI Stage | Definition |
|---|---|
| **0** | No significant change in creatinine |
| **1** | ↑ SCr by 0.3 mg/dl within 48 h or↑ in SCr by 150% to 200% from previous trough |
| **2** | ↑ in SCr by 200% to 300% of previous trough |
| **3** | ↑ in SCr 300% of previous trough or SCr 2.5 mg/dl or RRT |

SCr = serum creatinine. [9]

**Table (3)** Comparison between Group I and Group II regarding Mode of Delivery, demographic data, Resuscitation Effort and apgar 1m and apgar 5m

| | | | Group I | Group II | $X^2$ | P. value |
|---|---|---|---|---|---|---|
| **Mode of Delivery** | **CS** | **No.** | 41 | 44 | 0.706 | .401 |
| | | **%** | 82.0% | 88.0% | | |
| | **NVD** | **No.** | 9 | 6 | | |
| | | **%** | 18.0% | 12.0% | | |
| **Apgar 1m** | **Mean ± SD** | | 3.62 ±1.55 | 3.46 ± 0.95 | 0.622**t.test** | 0.535 |
| **Apgar 5m** | **Mean ± SD** | | 7.46 ± 0.84 | 7.60 ± 0.67 | -0.923**t.test** | 0.359 |
| **Sex** | **female** | **No.** | 22 | 20 | 0.164 | 0.685 |
| | | **%** | 44.0% | 40.0% | | |
| | **male** | **No.** | 28 | 30 | | |
| | | **%** | 56.0% | 60.0% | | |
| **Gestational Age (wks.)** | **Mean ± SD** | | 32.58 ± 1.76 | 34.76 ± 1.64 | -6.411**t.test** | 0.000 |
| **Birth Weight (kg)** | **Mean ± SD** | | 1.59 ± 0.39 | 2.25± 0.66 | -6.077**t.test** | 0.000 |

**Table (4)** Comparison between Group I and Group II regarding admission diagnosis.

| Admission Diagnosis | | Group I | Group II | $X^2$ | P. value |
|---|---|---|---|---|---|
| **congenital pneumonia** | **No.** | 1 | 3 | 0.260 | 0.609 |
| | **%** | 2% | 6% | | |
| **Respiratory distress** | **No.** | 42 | 34 | 2.686 | 0.101 |
| | **%** | 84% | 68% | | |
| **Transient tachypnea of newborn** | **No.** | 10 | 17 | 1.826 | 0.176 |
| | **%** | 20% | 34% | | |
| **Hypoxic ischemic encephalopathy** | **No.** | 0 | 1 | 1.010 | 0.314 |
| | **%** | .0% | 2.0% | | |

**Table (5)** Comparison between Group I and Group II regarding AKI.

| | | | Group I | Group II | t.test | P. value |
|---|---|---|---|---|---|---|
| **AKI** | **NO** | **No.** | 31 | 24 | 1.980 | 0.015 |
| | | **%** | 62.0% | 48.0% | | |
| | **YES** | **No.** | 19 | 26 | | |
| | | **%** | 38.0% | 52.0% | | |

**Table (6)** Comparison between Group I and Group II regarding KIDGO classification of AKI of at Day 7.

| | | | Group I | Group II | $X^2$ | P. value |
|---|---|---|---|---|---|---|
| **KIDGO classification of AKI at Day 7** | **0** | **No.** | 46 | 32 | 9.848 | 0.002 |
| | | **%** | 92.0% | 64.0% | | |
| | **1** | **No.** | 4 | 15 | 6.498 | 0.011 |
| | | **%** | 8.0% | 30.0% | | |
| | **2** | **No.** | 0 | 3 | 1.375 | 0.041 |
| | | **%** | .0% | 6.0% | | |
| | **Mean ± SD** | | .08± .274 | .42± .609 | -3.599 | .001 |

**4. Discussion**

The research revealed that, statistically, gestational age and weight were lower in Group I than in Group II (p value = 0.000).

These findings coincident with Sivasaranappa and Aara, [10], who showed that newborns with lower Gestational age and birth weight had received caffeine.

This is the same as the research of Harer et al. [11], which showed that neonates with younger gestational age and lower birth weight received caffeine.

This research revealed that there was no statistically significant difference in terms of method of delivery and sex between group I and group II.

Sivasaranappa and Aara [10] concurred that there was no statistically significant difference in delivery method and sex between group I and group II.

This was confirmed with Carmody et al., [7], who found that there were no statistically significant differences in the method of delivery and sex between the investigated groups.

This research revealed no statistically significant difference in Apgar score between Group I and Group II between 1 and 5 minutes.

This contrasted with Sivasaranappa and Aara, who [10] reported that neonates not receiving caffeine had higher Apgar scores at 5 minutes, nevertheless, the difference between groups at 1 minute was statistically significant.

This research revealed that respiratory distress is the most frequent diagnosis of admission among all premature newborns examined.

This is in agreement with Khasawneh et al. [12], who identified the newborn's respiratory distress, which was the primary indicator of admission for all instances examined.

This research shows that hypoxic ischemic encephalopathy was the least frequent diagnosis of admission among all newborns examined.

This was the least frequent diagnosis of admission among all newborns examined, in accordance with Khasawneh et al., [12] who reported hypoxic ischemic encephalopathy.

This research revealed that the difference in ventilation between Group I and Group II was statistically significant. (P.val.= 0.04)).

These findings coincided with Sivasaranappa and Aara [10], who showed that neonates using caffeine are more likely to need invasive or non-invasive assistance for their air.

This research revealed that 45 percent of the newborns in this study had been hospitalised to our neonatal intensive care unit (NICU).

AKI was characterised in our research at day 7 by modified neonatal kidney disease (KDIGO) staging [10].

It is in line with Jetton et al., [5], who showed that 30% of newborns hospitalised to an AKI-developed Neonatal Intensive Care Unit (NICU).

This finding was similarly confirmed by Kamath and Luyckx [13], who reported that 21% of all enrolled newborns had early AKI.

This is also in accord with Charlton et al., [14], who in the first postnatal week wanted to explain the risk factors and outcomes of newborn AKI. The worldwide retrospective observing cohort research, Assessing the Worldwide AKI Neonate Epidemiology (AWAKEN), comprised newborns hospitalised to a neonatal intensive care unit which received IV fluids for a minimum of 48 hours. They discovered that 21% (449 of 2110) had early AKI.

In the present research, 38 percent of AKI in the exposed group of caffeine was statistically significant less than AKI in the exposed group of non-caffeine (52 percent ). Wert P = 0.015

This was comparable to the findings of research by Harer et al. [11] that showed Acute kidney damage to neonates who consumed caffeine less often compared to non-neonates (P < 01). Caffeine is linked with decreased risk of AKI in preterm newborns.

These findings were consistent with Sivasaranappa and Aara, who [10] reported that neonates who took caffeine were less likely to suffer early AKI than those who did not develop it (17.5% vs 44.2%), p=0.004). Premature neonate coffeine treatment is linked with decreased incidence and severity of AKI. Due to the positive benefits of caffeine, regular usage in preterm newborns may reasonably be considered to avoid or decrease AKI.

This was consistent also with Carmody et al., [7] who reported that a single-centre retrospective analysis of very low birth weight (VLBW) neonates (birth weight, <1500g) investigated whether exposure to caffeine might be linked with a reduction in the incidence of AKI.

In VLBW children, caffeine usage almost increased from 40% to 70% between 1997 and 2010, (Dobson et al [15].

Biologically plausible is the notion that coffee may prevent or decrease the severity of AKI. As previously stated, theofylline may attenuate AKI in certain newborn groups and existing KDIGO recommendations on clinical practise indicate that neonates with severe prenatal hypoxia, which are at high risk of AKI, get a single dosage. [16] Caffeine and theophylline are methyl xanthine-like structurally and share a mode of action as non-selective adenosine receptor antagonists. Extracellular adenosine acts as a signalling molecule in addition to its well-known intracellular activities. Adenosin production rises over time when oxygen is restricted and may assist to preserve cell function or reduce inflammation during times of hypoxic stress. [17] Adenosine's function in AKI has been examined lately. The activation of glomerular adenosine A1

receptor induces afferent arteriole vasocontrol after ischemical renal tubular injury which leads to a reduction in GFR retention and salt and water retention. This system may evolutionarily benefit from tubuloglomerular feedback, but the short term impact of fluid retention and electrolyte disturbances can add to the morbidity and mortality of AKI in contemporary hospitalised patients. [18] There have been more mixed human clinical trials and there is at least theoretical worry that antagonism of adenosin may increase the consumption of cellular oxygen and prolong renal damage with AKI. [19] A meta-analysis of randomised, controlled trials showed that theophylline decreased contrast-induced AKIs in the general population [20] beyond the positive theophylline studies in newborns. A wide clinical study of the rolofylline, the selective A1 receptor antagonist, did not find any advantage for extended life or better renal function in individuals suffering from cardiorenal syndrome. [21] These inconsistent findings indicate that the therapeutic usefulness of adenosine antagonism is important not only for the medication but also the patient group and the cause of AKI.

The connection between caffeine and AKI may possibly not be caused by any confusion or intrinsic activity in the kidneys but is mediated by favourable non-renal effects of caffeine. While the significance of caffeine in the treatment of newborn apnea has long been known by neonatologists, there are growing indications of short-term or long-term advantages of caffeine for many other organisms. [22].

## 5. Conclusion

Caffeine administration to preterm infants is associated with reduced incidence of AKI**.**

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