RISK FACTORS OF ACUTE KIDNEY INJURY IN ADMITTED NEWBORNS IN THE NEONATAL INTENSIVE CARE UNIT

By

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ABSTRACT

Background: *Acute Kidney Injury (AKI) in the newborn is a common problem in the neonatal intensive care unit. The incidence of acute kidney injury ranges from 6-24%* ***(Andreoli, 2016)***.

Aim: *This study aimed to study the risk factors for the development of acute kidney injury in admitted newborns in the neonatal intensive care unit.*

Patients and methods: *The study was a simple random study.*

The study was carried out on 150 neonates, who were admitted to the neonatal intensive care unit (NICU) of Al-Azhar University Hospitals (Al-Hussien and Sayed Galal hospitals) during the period from November 2018 to August 2019.

Results: *The study showed that the most common risk factors of neonatal acute kidney injury is sepsis, prematurity, hypoxic ischemic encephalopathy (HIE) and respiratory distress syndrome.*

Conclusion: *The study concluded that the main risk factors for AKI in these neonates were sepsis, prematurity, HIE and respiratory distress.*

INTRODUCTION

Acute Kidney Injury (AKI) in the newborn is a common problem in the neonatal intensive care unit. The incidence of acute kidney injury ranges from 6-24% **(Andreoli, 2016)**.

AKI is the rapid decline in the kidney ability of maintaining homeostasis of water and electrolytes associated with a reduction of the glomerular filtration rate. AKI in term newborns within the first few days of life refers to progressive increment in plasma creatinine by higher than 1.5 mg/dl for at least 24-48 h, if a mother has normal kidney function **(Avery et al, 2005**; **Vogt and Avner 2006)**.

It is a complex disorder with clinical manifestation ranging from mild dysfunction to complete anuric kidney failure **(David et al, 2018)**. Oliguria is defined as urine output < 1 ml/Kg/hr, so that patients with acute renal failure (ARF) are subdivided into oliguric and non-oliguric. Reduction of urine cannot be the only criterion for ARF **(Csaicsich et al, 2017**; **Andreoli, 2017)**.

Aims of the Work

The aim of this study was to investigate the risk factors and causes for development of acute kidney injury (AKI) in neonatal intensive care units (NICU).

Ethical consideration:

- Written Parent consent for the study was obtained before the study.
- Approval of the local ethical committee in the pediatrics department, college and university were obtained before the study.
- The authors declaired no potential conflict of interest with respect to the research & publication of this article.
- All the data of the patient & results of the study are confidential & the patient has the right to keep it.
- The authors received no financial support for the research & publications of the article.

PATIENTS AND METHODS

The study was carried out on 150 neonates, who were admitted to the neonatal intensive care unit (NICU) of Al-Azhar University Hospitals (Al-Hussien and Sayed Galal hospitals) in the period from November 2018 to August 2019.

The study was a simple random study.

Inclusion criteria:

All neonates admitted at the neonatal intensive care unit (NICU) of Al-Azhar University Hospitals (Al-Hussien and Sayed Galal hospitals) for any medical condition suggesting AKI. e.g oliguria, elevated serum creatinine, hypertension.

Exclusion criteria:

Neonates presenting with congenital anomalies of the kidneys and the urinary tract were excluded from the study.

The studied neonates were subjected to the following:

Clinical Study:

This included complete history taking including antenatal, natal and post natal history then complete physical examination was done.

Laboratory Investigations:

1. Complete blood count with differential.
2. C-reactive protein (mg/l).
3. Blood culture.
4. Arterial blood gases.
5. Serum blood urea nitrogen (mg/dl).
6. Serum creatinine (mg/dl).
7. Serum electrolytes like sodium, potassium and calcium.
8. Serum Cystatin C (mg/l).
9. Urine analysis.

Imaging:

Abdominal ultrasound was done as possible to search for any abnormal size, shape, or echogenicity of the kidney.

According to the lab results the studied neonates were subdivided into two groups:

Group 1: included 30 neonates with acute kidney injury AKI.

Group 2: included 120 neonates without acute kidney injury.

Statistical analysis:

All collected questionnaires were revised for completeness and consistency; recorded data was entered on the computer using Microsoft office excel software program 2010 for windows. Statistical social package for social science (SPSS) program version 10 was used for analysis of data.

Data was summarized using mean and standard deviation (if parametric) or median and interquartile range (if non parametric) for quantitative variables and frequency and percentage for qualitative ones.

P-values less than 0.05 were considered statistically significant and less than 0.001 were considered highly significant.

RESULTS

Table (1): Average urine output of the studied neonates

Urine Output	Group 1 (n=30)		Group 2 (n=120)		
UOP (ml/ kg /hr).	Mean±SD	Median	Mean±SD	Median	P-value
	1.7±0.8	1.9	2.2±0.8	2.0	**0.036***

This table shows that there is significant statistical difference between the studied groups as regarding urine output (p-value= 0.036).

Table (2): Laboratory findings of the studied neonates

Laboratory findings	Group 1		Group 2		
	Mean±SD	Median	Mean±SD	Median	P-value
Urea (mg/dl)	58.2±19.5	48.5	23.7±14.2	20.0	<0.001*
Creatinine (mg/dl)	2.2±0.8	1.66	0.64±0.23	0.70	<0.001*
Cystatin C (mg/l)	1.92±0.57	1.76	0.69±0.14	0.52	<0.001*

This table shows that there is significant statistical difference between the two groups as regarding serum urea, creatinine and Cystatin C with p-value <0.001.

Table (3): Demographic data of the studied neonates

	Group 1		Group 2		
	N (30)	%	N (120)	%	P-value
Sex:					
F	17	56.6%	60	50 %	0.654
M	13	43.4%	60	50 %	
Maturity:					
FT	16	53.33%	72	60 %	0.348
PT	14	46.67%	48	40 %	
Mode of delivery					
CS	25	83.33%	84	70%	0.287
NVD	5	16.67%	36	30%	
	Mean±SD	Median	Mean±SD	Median	P-value
Maternal age (years)	26.3±5.5	26.8	27.7±3.7	27.0	0.523
Post natal age (days)	3.5± 2.7	1.6	4.2±3.3	2.1	0.458

This table shows that there is no significant statistical difference between the studied groups as regarding demographic data.

Table (4): Risk factors of AKI among the studied neonates

Risk factors	Group 1		Group 2		P-value
	No (30)	%	No (120)	%	
Sepsis	16	53.30%	56	46.70%	0.551
Prematurity	14	46.67%	48	40.00%	0.456
RDS	8	26.67%	36	30.00%	0.541
CHD	6	20.00%	20	16.67%	0.697
PROM	5	16.67%	20	16.67%	1.000
PPHN	3	10.00%	8	6.67%	0.682
Shock	2	6.67%	8	6.67%	1.000
HIE	4	13.33%	4	3.33%	**0.042**
IUGR	2	6.67%	12	10%	1.000
IVH	1	3.33%	8	6.67%	0.652

N.B.: One patient may have more than one disease.

This table shows that there is no significant statistical difference between the studied groups as regarding risk factors of AKI except HIE which shows significant statistical difference ($p = 0.042$).

DISCUSSION

Neonatal kidney diseases could be presented in many aspects; the most important is AKI which is a complex disorder with clinical manifestation ranging from mild dysfunction to complete anuric kidney failure **(Bellomo et al., 2004)**. Several studies had shown that AKI is common in the neonatal intensive care unit, the incidence of acute renal failure ranges from 6 - 24% **(Andreoli, 2016)**.

The study was carried out on 150 neonates who were admitted to the NICU of Al Azhar University hospitals during the period from November 2018 to August 2019 searching for the risk factors of AKI. These neonates were fully investigated then subdivided in to 2 groups:

Group 1: included 30 neonates with acute kidney injury.

Group 2: included 120 neonates without acute kidney injury.

Our study showed that there is female predominance, whereas **Mortazavi et al., 2009** reported that there is male predominance, where male: female ratio is 2:1. Other studies revealed female predominance like **Evlijana and Devleta, 2015** who reported that 87.8 % were females.

In our study, full term neonates (53.33 %) were more frequent than preterm neonates (46.67 %). **Mortazavi et al., 2009** reported that full term neonates (70.2 %) were more frequently accompanied by AKI than preterm neonates (25 %). Also **Momtaz et al., 2014** reported that 79.5 % of the patients were full term, but other studies like **Youssef et al., 2015** showed that 59.3 % of the patients were preterm.

Our study shows that sepsis (53.3 %) and respiratory distress syndrome (26.67 %) were the most frequent conditions accompanying AKI in our study. In **Youssef et al., 2015** study, the most common predisposing factors were sepsis (63 %) and respiratory distress syndrome (55.6 %), and in **Evlijana and Devleta, 2015** sepsis was the most common cause of AKI 71.5 %. Also **Subramanian et al., 2008** reported that sepsis and perinatal asphyxia were the most common associated conditions, while **Cuzzolin et al., 2006** reported that the cause of AKI in neonates is multifactorial. On the other hand other studies like **Agras et al., 2004** showed that sepsis occurred in 22.2 % in their patients, and **Mathur et al., 2017** in India showed that 26 % of septic neonates developed AKI; also **Mortazavi et al., 2009** reported that sepsis occurred in 28.5 %.

A variety of mechanisms including shock, disseminated intravascular coagulation, hemorrhage and cardiac failure may cause AKI in septic neonates **(Mathur et al., 2006)**.

It should be noted that our country is a developing one with overcrowding and low ratio between the nurses and the patients which may lead to improper application of infection control measures. This could explain the high percentage of sepsis; thus sepsis is the most common predisposing factor of AKI in our study, therefore infection control measures pre-, intra-, and postnatal are of utmost importance to overcome this high rate of neonatal sepsis with its high incidence of morbidity and mortality.

Hypoxic ischemic encephalopathy was detected in 13.33 % of patients in our study. In other studies perinatal asphyxia has been considered as the most prevalent cause of AKI higher than sepsis like **Mortazavi et al., 2009** who reported that perinatal asphyxia was detected in 29.8 % of their patients and **Evijana and Devleta, 2015** who showed that perinatal asphyxia was seen in 42.8 % of cases. Also **Nouri et al.,**

2008 observed AKI in 17.2 % of neonates who were admitted for hypoxic ischemic encephalopathy.

The limitation in renal tissue oxygen supply renders the kidney susceptible to hypoxia and has long been recognized as an important factor in the pathogenesis of AKI **(Eckardt et al., 2005)**. Because AKI associated with asphyxia is predominantly non-oliguric, the serum creatinine level should be monitored daily in severely asphyxiated neonates **(Gouyon and Guignard, 2000)**.

The mean and SD of UOP in our study was 1.7 + 0.8ml/kg/hr, which is significantly lower in cases than in controls (p-value = 0.043). This revealed that most of our AKI patients were non-oliguric, where oliguria is defined as UOP <1 ml/kg/hr **(Srisawat et al., 2010)**. Similarly, **Youssef et al., 2015** reported that non-oliguric AKI was more frequent than oliguric AKI with 29.6 % of patients being oliguric. **Mathur et al., 2006** also indicated that AKI developed in 26 % of newborns, from which 15 % were oliguric, therefore it should be noted that serum creatinine level should be monitored in patients with suspected AKI regardless UOP otherwise, cases with AKI would be missed specially the non-oliguric ones. But other studies like **Mortazavi et al., 2009** reported that the incidence of oliguric AKI in neonates was 72.2 % and **Momtaz et al., 2014** showed that oliguric AKI was more prevalent.

The mean and SD of the average level of serum urea level in our study was 58.2 + 19.5 mg/dl, which is significantly higher in cases than in controls (p-value <0.001), and the mean and SD of the average level of creatinine was 2.2+ 0.8mg/dl which is significantly higher in cases than in controls (p-value < 0.001). Also **Ahmed et al., 2014** reported that the mean and SD of BUN was 40.8 + 11.4 (p-value <0.05) and the mean and SD of creatinine was 1.3 + 0.3 (p-value <0.05), whereas the level of BUN and creatinine was not as low as **Viswanathan et al., 2012** who reported that the mean and SD of BUN was 8.46 + 44 (p-value = 0.3) and the mean and SD of creatinine was 0.35 + 0.11 (p-value = 0.6), also the level of BUN and creatinine was not as high as in **Mortazavi et al., 2009** who reported that the mean and SD of BUN was 74.2 + 29.3 and the mean and SD of creatinine was 3.98 + 2.4. In Our study, 50 % of patients were treated by vancomycin, 26.70 % by amikacin, 43.33% by fluconazole

also other medications where 16.7 % were treated by diuretics, 43.33% by inotropes, 46.67 % by benzodiazepines and 26.67 % by xanthines. This may be due to high percentage of sepsis and the over-use of antibiotics among our patients. Although the literature reported that nephrotoxic medications have a role in AKI in neonates, yet the values are not significant in our study, this may be due to the low efficacy of antibiotics because of the over-use of antibiotics in our patients. **Cataldi et al., 2005** demonstrated that infants with AKI were subjected to long term exposure to antibiotics, NSAIDs and diuretics. The use of midazolam has been associated with hypotension and oliguria. Also **Viswanathan et al., 2012** showed that infants with AKI had a higher postnatal exposure to cefotaxime, benzodiazepines, diuretics and inotropes prior to development of AKI. The higher exposure to cephalosporins prior to AKI is consistent with previous reports **(Cataldi et al, 2005)**. Most cephalosporins are safe for use in newborn infants; however at extremely high levels third generation cephalosporins which are the most common dugs used to treat newborn infants cause renal damage **(Fanos et al., 2010)**.

CONCLUSION

The study concluded that the main risk factors for AKI in these neonates were sepsis, prematurity, HIE and respiratory distress while HIE is the most significant risk factor.

RECOMMENDATIONS

1. Proper antenatal care and early management of maternal illnesses during pregnancy to decrease their effect on the newborns.
2. Infection control measures – pre-, intra-, and post natal are of outmost importance to overcome this high rate of neonatal sepsis with its high incidence of morbidity and mortality.
3. Renal function tests and urine output monitoring should be fixed in the plan of management of each neonate in NICU who are at risk of development of AKI.
4. All babies who develop AKI need urgent management and follow up. Adequacy of nutrition, blood pressure, and renal function status has to be monitored. As the newborn that develop AKI are predisposed to development of chronic kidney disease in the future.

5. Large studies are needed to test definitions and better understand risk factors, incidence, independent outcomes, and mechanisms that lead to poor outcomes of neonatal renal disorders.

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دراسة عوامل الخطر للاصابه بالقصور الكلوي الحاد في الأطفال حديثي الولادة المحجوزين فى الرعاية المركزة للاطفال حديثى الولادة

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يعتبرالقصور الكلوي الحاد اعتلالا جسديا تتراوح فيه الاعراض الاكلينيكية من تاثر وظيفى خفيف الى فشل كلوي تام. يعد القصور الكلوى الحاد في الأطفال حديثي الولادة مشكلة سائدة في وحدة الرعاية المركزة لحديثي الولادة.

تعد هذه الدراسة دراسة استطلاعية للتحقيق في الاسباب والعوامل التى تؤدى الى القصور الكلوي الحاد. شملت الدراسة150 مريضا بوحدة الرعاية المركزة لحديثي الولادة بمستشفيات جامعة الأزهر بالقاهرة، خلال الفترة من نوفمبر 2018 الى أغسطس 2019 و قد خضع هؤلاء الاطفال حديثى الولادة الى ما يلى: التاريخ المرضى كاملا والفحص الطبى الشامل للمريض و التحاليل و الاشعات اللازمة مثل العد الكامل للدم، بروتين سي التفاعلي، مزرعة دم، غازات بالدم الشرياني، الكرياتينين واليوريا في الدم، نسبة الصوديوم، البوتاسيوم، والكالسيوم بالدم، تحليل البول وعمل الموجات فوق الصوتية على البطن و ايضا العلاج اللازم من تدخلات وأدوية تعطى للمرضى ولقد تم تقسيم هؤلاء المرضى إلى مجموعتين،

مجموعة الحالات المرضيه التى شملت 30 مريضا اصيبوا بقصور كلوى حاد و مجموعة الضابط التى شملت 120 مريضا لم يصابوا بقصور كلوى حاد.

و لقد أظهرت الدراسة أن أمراض الأمهات مثل ارتفاع ضغط الدم، والسكري، وأمراض القلب الروماتيزمية وفقر الدم كانت عوامل خطورة لحدوث القصور الكلوي الحاد لحديثي الولادة، حيث كان يعانى 13.33٪ من الأمهات من فقر الدم و16.67٪ من ارتفاع ضغط الدم و10٪ من مرض السكرى، 6.67٪ من الحمى الروماتيزمية بالقلب و 3.33٪ من فقر الصفائح الدموية. وكانت عوامل الخطر الرئيسية لقصور الكلى الحاد عند هؤلاء حديثى الولادة هى التسمم الدموى, نقص النمو, نقص الاكسجين بالمخ والضيق في التنفس حيث يمثل تسمم الدم 53.30٪ من الحالات، يمثل نقص النمو 46.67٪ من الحالات، ويمثل الضيق فى التنفس 26.67٪ من الحالات.

كما أظهرت الدراسة أن الأدوية المؤثرة على الكى لها دور في حدوث قصور كلوى حاد في حديثي الولادة مثل المضادات الحيوية، حيث تم علاج 50٪ من قبل الفانكومايسين،43.33% من قبل الفلوكونازول و26.70٪ من قبل الأميكاسين وأيضا تم علاج 16.7٪ من قبل مدرات البول، و 43.33٪ من قبل مقويات عضلة القلب، 46.67٪ من قبل البنزوديازيبينات و 26.67٪ من قبل الزانثينات.

و خلاصة الدراسة أن أمراض الأم كانت من أهم عوامل الخطورة للإصابة بقصور الكلى الحادة في الأطفال حديثي الولادة و كان التسمم الدموى ونقص النمو و نقص الاكسجين بالمخ و ضيق التنفس ايضا من العوامل الخطر الرئيسية للاصابة بالقصور الكلوى الحاد في هؤلاء الاطفال.

يوصى بمتابعة جميع حالات الرعاية المركزة لحديثي الولادة من ناحية وظائف الكلى و خاصة للحالات الأكثر عرضه لحدوث القصور الكلوي الحاد مع العلاج السريع لتفادي المضاعفات.