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Incidence and risk factors of acute kidney injury among the critically-ill neonates

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Running Title: *Acute Kidney Injury in NICU*

Abstract:

Background: Acute kidney injury (AKI) is a complex disorder with clinical manifestations ranging from mild dysfunction to complete kidney failure. Research on incidence and outcomes of AKI in the critically ill neonatal population is scarce. The aim of the study was to evaluate the types, the associated risk factors and short-term outcome of AKI in the critically-ill neonates.

Methods: A cohort study was conducted including 100 critically ill neonates successively admitted to NICU. Inclusion criterion was a gestational age ≥28 wk, and body weight ≥ 1kg. Exclusion criteria included those with multiple congenital anomalies, or on drugs altering glomerular filtration rate (GFR) or AKI developing postoperatively. Neonates were evaluated for the development of AKI (creatinine >1.5 mg/dl and/or BUN >20 mg/dl) and were assigned as group A (developed AKI) and group B (did not develop AKI).

Results: 41 developed AKI (Group A) where 9 (22%) showed oliguric AKI. The most common risk factors among group A were sepsis (75.6%) and nephrotoxic drug administration (75.6%), followed by shock (39%). There were no statistically significant differences between both groups except for the male sex predominance and necrotizing enterocolitis (NEC), which were significantly higher among group A ($p<0.05$). CPAP ventilation was significantly higher in neonates without AKI (13.6% vs 0.0%, $p=0.02$). The mortality rate among group A reached 51.2%.Various risk factors including gender, gestational age, birth weight, shock, NEC, sepsis, nephrotoxic drugs, oliguria and

mechanical ventilation were studied as regards outcome of group A, and all factors except gender and oliguria proved to be significantly higher in deceased neonates.

Conclusion: Male sex and NEC were important risk factors for developing AKI that was predominantly non-oliguric. CPAP may have a protective effect against AKI. The mortality rate was more than three times higher in AKI group.

Introduction

Acute kidney injury (AKI) is a complex disorder with clinical manifestation ranging from mild dysfunction to complete anuric kidney failure. The lack of a universal definition for AKI, till recently, has rendered comparative studies limited and harder to achieve ***(1)***. Acute kidney injury in the newborn is a common problem in the neonatal intensive care unit (NICU) and ranges from (6 – 24%) ***(2),(3).***Many underlying factors may contribute in AKI development such as asphyxia, respiratory distress syndrome, and urogenital anomalies ***(4***). In a full term neonate, the kidney functions are not fully mature and functional maturation continues in the postnatal age. Under normal circumstances, the kidneys adapt to various endogenous and exogenous stresses. However, in sick neonates and in stressful conditions like sepsis and shock the adaptive capacities of the kidney may be overcome leading to renal dysfunction ***(5)***. Permanent renal damage may develop in survivors of AKI in up to 40 % of cases ***(6***). The aim of this study was to investigate the incidence of AKI in a single tertiary center and to evaluate the risk factors that could be correlated with developing AKI in sick neonates. We supposed that the risk factors may include sepsis, shock, and congestive heart failure, premature rupture of membrane, necrotizing enterocolitis (NEC), nephrotoxic drugs and mechanical ventilation.

Patients, materials and methods

This was a cohort study of 100 critically-ill neonates admitted to Cairo University, Children's Hospital NICU, that were enrolled successively during a period from August 2009 to February 2010. The basic inclusion criterion was admitted newborns with gestational age ≥28 wk, and body weight ≥ 1kg. Exclusion criteria included neonates with multiple congenital anomalies, neonates with postoperative AKI, neonates on drugs altering glomerular filtration rate (GFR) (e.g. ACE inhibitors or indomethacin) and neonates with maternal history of kidney failure. The study protocol was approved by Cairo University Children's Hospital Investigational Review Board and was conducted in accordance with the University bylaws for human research. Verbal consent was taken from all newborn's legal guardians before enrollment.

Enrolled neonates were 60 males (60%), 40 females (40%) with a mean gestational age of 35.9±2.9 wks (range 28-38). Patients were assigned into two groups: group A: which included 41 critically–ill neonates who developed AKI and group B which included 59 cases that didn't develop AKI. AKI was defined as serum creatinine (Cr) > 1.5 mg/dl ***(7)***,(***8)***,(***9)***,(***6***), and/or blood urea nitrogen (BUN)> 20mg/dl ***(4)*** on two separate occasions at least 12 hours apart.

Methods

For all 100 neonates, a detailed perinatal history including Maternal illness as hypertension, diabetes mellitus and drug administration, mode of delivery, Apgar score at 1 and 5 minutes of delivery, history of cyanosis or convulsions. Physical examination

was carried out upon entry into the study with thorough clinical examination of all systems. We recorded the administration of known nephrotoxic drugs (vancomycin, amikacin and gentamycin) during hospital stay, in addition to the mode of ventilation if any (nasal continuous positive airway pressure (CPAP), synchronized intermittent mandatory ventilation (SIMV). The patient who was on CPAP then SIMV or SIMV then CPAP was considered as he was on SIMV in the results.

The risk factors studied for the occurrence of AKI included sepsis, shock, heart failure, NEC, nephrotoxic drug administration and mechanical ventilation.

From patients who developed AKI (group A), the following labs were sampled on the day of admission, on peak of renal impairment and on discharge: CBC , CRP, BUN, Cr, Na, K, Ca, PO4. For group B, same investigations were sampled initially and on discharge only.

Peak renal impairment was defined as the point with highest Cr and or necessitating dialysis. Oliguria was defined as urine output < 1 ml/Kg/hr ***(4)***. Urine output was monitored all through the study, but values recorded in the results were those during the peak of renal impairment , while in case of initiation of dialysis, urine output recorded was that of the 24 hours preceding dialysis. GFR was measured using the Scwartz formula: Estimated GFR= (k x Height)/ serum creatinine, where k is a constant that equals 0.33 and 0.45 in prematures and full terms respectively in their 1^{st} year of life ***(10), (11).*** On discharge, GFR was plotted against normal values for age in term and preterm neonates to be evaluated whether discharged with normal or impaired GFR ***(12),(13).***

Sepsis was diagnosed on the basis of either a positive sepsis screen or a positive blood culture in symptomatic neonates. The screen was considered positive if 2 or more of the following were present: immature / total (I: T) neutrophil ratio > 0.2 (Immature neutrophils include Band cells + myelocytes + metamyelocytes which increase as bone marrow pushes even the premature cells into circulation, to fight infection) , micro-ESR > age in days + 2 mm or> 15 mm, CRP> 6 mg/dl, TLC< 5000 cells/mm³ ***(4)*.**Necrotizing enterocolitis was assessed according to modified Bell's staging criteria into 3 stages ***(14).***

Outcome Measures: Primary outcome variables were survival or death. The main secondary outcome variable for survivors included discharge with normal or impaired GFR

Statistical methods: Data management and analysis were performed using SigmaStat program; version 3.5 (Systat Software, Inc., USA). The numerical data were statistically presented in terms of median and interquartile range. Categorical data were summarized as percentages. Comparisons between numerical variables of groups were done by Mann-Whitney rank sum test. Comparing categorical variables were done by Chi square ***(15)*** or Fisher exact test for small sample size. Z-test (at a confidence interval of 95%) was used for comparing single proportions. All P values are two tailed and considered significant when less than 0.05.

Results

The 100 critically-ill neonates enrolled were 60% males and 40% were females with a median gestational age of 38 weeks (IQR: 34-38) .The demographic and baseline data of the studied cases are illustrated in table 1.

Out of the 100 critically-ill babies included in our study group; 41 developed AKI (group A) with BUN ranging from 4 to 254 mg/dl and Cr ranging from 0.1 to 14.6 mg/dl while those who did not develop AKI constituted group B. (table 2). In group A, neonates with low (normal) Cr had, on the other hand, serum BUN >20 mg/dl and suffered from pre renal insults as shock and sepsis (their Cr: BUN >20). Out of the 41 cases with AKI (group A), 9 neonates (22%) were oliguric while the remaining 32 (78%) neonates were non-oliguric. No significant difference in median urine output was observed between group A (2 ml/Kg/hr ranging from 1.175-2.750 ml/Kg/hr) and group B (2 ml/Kg/hr ranging from 1.725-2.600 ml/Kg/hr) (P = 0.2).

Five patients (8.5%) of group B had elevated Cr on discharge (1.4 mg/dl in 3 cases and 1.5 mg/dl in 2 cases) but were not considered in AKI group (Cr not > 1.5 mg/dl and BUN not > 20mg/dl as previously defining AKI). Table 2 illustrates the differences in kidney functions and serum electrolytes between group A and group B.

A comparison of the risk factors between group A and B is given in Table 3. The most common risk factors in group A were sepsis (75.6%) and nephrotoxic drug administration (75.6%), followed by shock (39%). However, there were no statistically significant differences between both groups except for the male sex predominance and prevalence of NEC which were significantly higher among group A ($p<0.05$). Presence of more than one risk factor was evident in all neonates of group A. It was observed that CPAP ventilation was significantly higher in neonates of group B (13.6% vs 0.0%, p=0.02).

Among neonates who developed AKI; twenty-one (6 girls and 15 boys; 51.2%) died during their hospital stay in the NICU, 10 (24.4%) were discharged with normal kidney

function, and 10 (24.4%) were discharged with impaired kidney function. A comparison of the outcome between group A and B is summarized in table 4.

Various factors were studied in group A as regards the outcome (whether survival or death). Several factors were proved to be significantly higher in deceased group while gender and oliguria did not affect the mortality. Sepsis was significantly more frequent in the patients who died than in those who survived (p=0.03). Also, of 23 patients who needed mechanical ventilation, 18 died (44%). This rate was significantly higher than in those who did not need mechanical ventilation (P = <0.001).

Discussion

Many physiologic factors render the The kidneys of neonates particularly susceptible to hypoperfusion,including low GFR,decreased intercortical perfusion,high renin activity and high renal vascular resistance. Sodium handling also is impaired with decreased Na reabsorption in the proximal tubules. ***(4)***. Thus, newborn infants are vulnerable to acute tubular necrosis or cortical necrosis ***(16)***. Critically ill neonates are at a greater risk of having AKI, as they are commonly exposed to nephrotoxic medications and have frequent infections that lead to multi-organ failure ***(17).***

The present study has analyzed AKI in the critically–ill newborn. It gives insight into the incidence, short term outcome and the independent impact of AKI on outcome in the critically-ill neonates.

The exact incidence of neonatal AKI is unknown. Though published studies estimate that the incidence of AKI in critically ill neonates is lower than that in our study(between 8%

and 24% ***(17)*** however, higher rates were reported in asphyxiated neonates with low Apgar scores ≤6 at 5 min (47- 56% vs 4% in controls) ***(6)***,***(9).***

It is worth noticing that AKI was mainly non-oliguric in the current study (oliguria was found only in 22%) and no significant difference in median urine output was observed in newborns with and without AKI. Other previous studies reported the presence of non-oliguric AKI to over 50%***,(6),(9), (18).***while Mathur and colleagues reported up to 85% of AKI patients to be non-oliguric ***(4)*** . Non-oliguria as well, was not correlated with outcome (mortality or survival) in our study. This confirms the non-innocence nature of AKI in sick neonates where a high index of anticipation should be raised, in spite of non-oliguria, especially in the presence of other risk factors ***(19)*** .Different studies reported higher incidence of non-oliguric AKI in asphyxiated neonates and recommended to monitor serum Cr daily and not to be satisfied with adequate urine output in asphyxiated neonates ***(16)*** .

Non-oliguric AKI, in part, could be attributed to the associated tubular injury accompanying AKI in vulnerable neonatal kidneys ***(20)*** which also may explain the discrepancy in the rise of creatinine and BUN without a concomitant rise of K and Phosphorus.

Among 41 newborns of group A, almost half were deceased. Survivors were equally divided between complete recovery and persistently impaired GFR on discharge. Different studies report poor survival in neonatal AKI. ***Agras et al.*** reported a 25% hospital mortality rate for neonates with AKI ***(8)***, while ***Gupta et al.*** reported a 14.1% mortality in infants with Apgar scores ≤6 ***(6)***.

This work aimed at studying the underlying risk factors in neonatal AKI. The development of AKI among the critically-ill neonates seems multi-factorial as the same risk factors in a same setting may affect newborns differently. Investigators suggested that the presence of underlying genetic risk factor(s) promoting the development of AKI including the combination of polymorphisms of tumor necrosis factor alpha, interleukin (IL) 1b, IL6, IL10 genes which might lead to a greater inflammatory response and the development of AKI in some neonates with infection ***(21)*** **.**

In our study we observed significant male sex predominance as a risk factor among cases that developed AKI; male-female ratio was (1.5:1). This was in line with Mortazavi and colleagues ***(16)*** who reported male-female ratio 2:1 in neonates with AKI. The high frequency of AKI in boys may be due to the susceptibility of boys to some perinatal disorders like sepsis and RDS ***(16)***.

Occurrence of NEC and mode of ventilation were other significant risk factors of AKI amongst our cases, while, gestational age, birth weight, sepsis, nephrotoxic drugs, congestive heart failure, premature rupture of membranes (PROM), perinatal asphyxia were not significant risk factors of AKI in the critically–ill neonates. This was in line with ***Mathur*** **and colleagues** ***(4)*** who reported similar results among septic cases who developed AKI. Though not statically significant, sepsis was the most common risk factor (75.6%) followed by nephrotoxic drug administration (75.6%), and shock (39%).Similar results were reported by *Pereira et al.* ***(22)*** and Mortazavi et al***. (16).***

In addition, there was a non-significant difference between AKI and non-AKI neonates as regard prevalence of mechanical ventilation in our study, which is not consistent with

previous studies ***(23),(24),(25)*** . Nevertheless, it was observed that CPAP ventilation was significantly higher in neonates without AKI (13.6% vs. 0.0%, p=0.02) raising the possibility of being a protective factor against AKI in the critically-ill babies. However a recent study reported higher prevalence CPAP among cases with AKI ***(25).***

In fact, our study have some limitations including being a single-center study and lacking a reliable consistent definition of AKI in the neonatal population. A larger population may have been needed to properly estimate prognostic predictors. Another limiting factor is lacking follow-up data of patients who were discharged and hence lacking data about the long –term outcome.

Conclusion

Male sex and NEC were important risk factors for developing AKI among our critically-ill babies. CPAP may have a protective effect against AKI. AKI was predominantly non oliguric. The mortality rate was more than three times higher in neonates with AKI; which demands a greater awareness of this entity among practitioners and better management of this condition. Low gestational age, low birth weight, low weight at presentation, shock, sepsis, nephrotoxic drugs and mechanical ventilation were proved to be significant risk factors in deceased neonates. Large multi-centre prospective studies are needed to test definitions and to better understand risk factors, incidence, independent outcomes, and mechanisms that lead to poor short- and long-term outcomes.

No conflict of interests is present in this study.

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Table 1: Demographic Features of The Study Group (n=100):

Studied cases (n=100)	
60 (60%) 40 (40%)	Sex (n, %) Male Female
35.859±2.928 (28-38) 38 (34-38)	Gestational age (wks) Mean ±SD (range) Median (IQR*)
40 (40%) 60 (60%)	Gestational age (n, %) Preterm Full term
2.308±0.754 (1-4.5) 2.4 (1.6-2.8)	Birth Weight (kg) Mean ±SD (range) Median (IQR)

*IQR: interquartile range.

Table 2: Comparison of The Biochemistry Profile Between Group A and Group B:

p-value	Group B (n=59)	Group A (n=41)	Contributing condition
<0.001*	11.0(9.0-15.0)	25.0 (11.750-44.75)	Blood urea nitrogen (mg/dl) Median (IQR)
<0.001*	0.4 (0.3-0.5)	0.9 (0.6-1.7)	Serum Cr (mg/dl) Median (IQR)
0.924	138.0 (135.0-142.0)	138.0(132.0-143.0)	Serum Na (mEq/l) Median (IQR)
0.633	5.4 (4.5-6.0)	5.0 (4.475-6.0)	Serum K (mEq/l) Median (IQR)
0.006*	8.9 (8.35-9.375)	8.1(6.925-9.0)	Serum Ca (mg/dl) Median (IQR)
0.389	4.0 (3.8-5.15)	4.5 (4.0-5.6)	Serum Phosphorus (mg/dl) Median (IQR)

*P- value is significant if <0.05

Table 3: Comparison of Patients' Variables between Group A and Group B:

p-value	Group B (n=59)	Group A (n=41)	Contributing condition
0.042*	30 (51%) 29 (49%)	30 (73%) 11 (27%)	Sex (n, %) Male Female
0.318	38.0(34.0-38.0)	38.0(32.0-38.0)	Gestational age (wks) Median (IQR)
0.967	23 (39%) 36 (61%)	17 (41.5%) 24 (58.5%)	Gestational age (n, %) Preterm Full term
0.844	2.3 (1.7-2.8)	2.7(1.5-3.0)	Birth Weight (kg) Median (IQR)
0.713	4 (7%)	4 (9.8%)	Perinatal asphyxia
0.319	15 (25.4%)	16 (39%)	Shock
0.041*	1 (1.7%)	5 (12%)	NEC**
0.101	34 (57.6%)	31 (75.6%)	Sepsis
0.799	10 (17%)	7 (17%)	CHF
0.918	52 (88.1%)	35 (85.4%)	Nephrotoxic drugs
0.017*	27 (45.8%) 8 (13.6%)	23 (56%) 0.0 (0.0%)	Mode of ventilation: SIMV CPAP

*P- value is significant if <0.05

** All NEC where graded stage I and II only

Table 4: Comparison of Outcome of Critically-ill Neonates with and without AKI:

P –value	Group B (n=59)	Group A (n=41)	
<0.001*	45 (76.3%)	10 (24.4%)	Normal GFR
	5 (8.5%)**	10 (24.4%)	Impaired GFR
	9 (15.2%)	21 (51.2%)	Death

*P- value is significant if <0.05

** Serum Cr higher than 1.0 and ≤1.5 mg/dl

Table 5: Comparison of Different Risk factors between Survivals and Deaths in Group A (n=41):

P-value	Died (n=21)	Survived (n=20)	
0.925	15 (71%) 6 (29%)	15 (75%) 5 (25%)	Sex distribution Male Female
0.044*	35.0 (30.8-38.0)	38.0(36.5-38.0)	Geastational age (wks)
0.023* 0.021*	2.038±0.751 2.0(1.3-2.7)	2.625±0.833 2.8(1.8-3.0)	Birth weight (kg)
0.023*	2.0 (1.3-2.725)	2.75 (1.75-3.0)	Weight at presentation (kg)
0.006*	13 (62%)	3 (15%)	Shock
0.343	4 (19%)	1(5%)	NEC
0.032*	19(90.4%)	12 (60%)	Sepsis
0.009*	21 (100%)	14 (70%)	Nephrotoxic drugs
0.13	7 (33.3%)	2 (10%)	Oliguria
<0.001*	18 (85.7%)	5 (25%)	Mechanical ventilation

*P- value is significant if <0.05