The Main Etiologies of Acute Kidney Injury in the Newborns Hospitalized in the Neonatal Intensive Care Unit

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ABSTRACT

Introduction: Acute kidney injury (AKI) is one of the most common diseases among the newborns hospitalized in the neonatal intensive care units (NICUs), which is usually resulted from predisposing factors including sepsis, hypovolemia, asphyxia, respiratory distress syndrome (RDS), and heart failure. The goal of this study was to assess main etiologies, relevant risk factors, and early outcome of neonatal AKI.

Materials and Methods: In a cross-sectional study, 49 consecutive neonates hospitalized in NICU of Besat hospital with diagnosis of AKI from October 2009 to October 2011 were investigated through census sampling method. AKI was diagnosed based on urine output and serum creatinine levels.

Results: The prevalence of AKI was 1.54% (49 out of 3166 newborns hospitalized in NICU) with the female: male was 7:1. Thirty-nine patients (79.5%) were full-term neonates. Oliguria was observed in 38 (77.5%) patients. Sepsis was the most common predisposing factor for AKI in 77.5% of patients (n = 38) accompanied with the highest mortality rate among other factors (30.5%). Other leading causes of AKI included hypovolemia secondary to dehydration, followed by hypoxia secondary to RDS, patent ductus arteriosus, posterior urethral valve, asphyxia, and renal venous thrombosis. A positive relationship was observed between neonates’ age, sex, urine output, and also between serum creatinine levels with initiation of dialysis. The mortality rate among the newborns hospitalized with AKI was 36.7%. Eighteen (36.7%) newborns were treated with peritoneal dialysis (PD) of whom 10 patients (55.6%) died, 31 patients were managed conservatively of whom five neonate died (25.9%).

Discussion: Prognosis of AKI in the oliguric neonates requiring PD is very poor. It is thus recommended to prevent AKI by predicting and rapid diagnosis of AKI in patients with potential risk factors and also by early and effective treatment of such factors in individuals with AKI.

Key words: Acute kidney injury, newborns, outcomes

INTRODUCTION

Acute kidney injury (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. Serum creatinine concentration in preterm infants in the first few days of life may not be a reflection of the glomerular filtration rate because creatinine rises during the first 36-96 h and then decreases gradually during the first 2 weeks. Incidence of AKI among NICU patients has been reported between 8% and 24% (1-7). Patients with AKI can be subdivided into oliguric (urine output of <1 ml/kg/h) and nonoliguric. Reduction of urine output is also observed in the absence of AKI, therefore it cannot be the only criterion for assessment.

Common causes of AKI in the neonates are: (1) Congenital malformations (including renal dysplasia, hypoplasia, agenesis and renal cysts); (2) acquired kidney diseases including acute tubular necrosis, vascular events (renal artery or vein thrombosis), or medications (angiotensin-converting enzyme inhibitor or indomethacin usage during pregnancy); and (3) obstructive uropathy.

Measurement of plasma creatinine level is the simplest and most practical mean for assessment of renal function. The plasma creatinine concentration immediately after term delivery declines gradually from 1.1 mg/dl (preterm neonate from 1.3 mg/dl) to 0.4 mg/dl during the first 2 weeks of life. Treatment of AKI includes conservative therapy, dialysis, and rarely surgery of urinary tract obstruction. In the newborns, peritoneal dialysis (PD) is preferred over other dialysis methods, especially in low-birth weight patients.

Some early outcomes observed in AKI of neonates include death and long-term hospitalization due to various...
conditions such as convulsion, uremic encephalopathy, and sepsis.

Considering the high incidence rate of AKI (8-24%) in hospitalized newborns and the high mortality rate of this disease (20-50%), it is one of the most important diseases among NICU patients.

The goal of this study was to assess main etiologies, relevant risk factors, and early outcome of neonatal AKI.

MATERIALS AND METHODS

In this cross-sectional study, all medical records of newborns hospitalized in NICU for 4 years between October 2008 and October 2011 were studied. AKI was diagnosed for hospitalized newborns, if serum creatinine level was >1.5 mg/dl. Necessary information such as demographic characteristics, radiology reports, treatment approaches, and early outcome (including death, long hospitalization due to various conditions such as oliguria, edema, hypertension, convulsion, bleeding, uremic encephalopathy, and sepsis) as well as duration of hospitalization were extracted from the medical records and registered in a predesigned form. AKI was divided into oliguric and nonoliguric and the early outcomes were registered as death and discharge. Data were compared using SPSS statistical software version 16.0 (SPSS Inc., IL, USA), and through descriptive statistical and inferential statistical methods including Chi-square test, Pearson’s correlation test and multiple linear regression analysis. P < 0.05 were considered as statistically significant.

RESULTS

In total, 49 out of 3166 neonates (1.54%) were diagnosed as AKI that consecutively entered into the study.

Of 49 AKI newborns, 43 (87.8%) were female and 6 (12.2%) were male. The average age of patients was 7.4 ± 6.2 days and the average weight of AKI babies was 3510 ± 680 g. 39 patients (79.5%) were full-term neonates. 24 cases (49.0%) were referred from townships of Hamadan province to Hamadan city. The mean duration of hospitalization for each newborn was 12.6 ± 1.0 days.

Average time required for normalization of creatinine for each newborn was 7.7 ± 6.3 days. Oliguria was detected in 38 patients (77.6%) and 11 newborns (22.4%), were nonoliguric.

The most common causes of AKI, in order of prevalence, included sepsis (77.5%), followed by hypovolemia secondary to dehydratation (46.9%), hypoxia secondary to respiratory distress syndrome (RDS) (34.6%), patent ductus arteriosus (PDA) (8.1%), posterior urethral valves (PUVs) (6.1%), asphyxia (4%), and renal venous thrombosis (RVT) (2%). Sepsis and incidence of AKI were significantly related (P = 0.03).

The most common complications were convulsion (38.7%), bleeding (16.3%), edema (14.2%), and hypertension (2%).

Death occurred in 18 patients (36.7%), while 63.3% were discharged with normal renal function [Table 1]. There was a significant relationship between neonates’ death and neonates’ gender, asphyxia, secondary hypoxia to RDS and dialysis [Table 2].

Serum creatinine level and age were both associated with the need for dialysis (P = 0.05) [Table 3].

Among all newborns studied, 37 (75.5%) had undergone sonography, which was reported as normal

| Variable          | Kidney injury (%) | P value |
|-------------------|-------------------|---------|
|                  | Oliguric | Nonoliguric |       |
| Gestational age   |          |            |       |
| Term              | 33 (84.6) | 6 (15.4)   | 0.01  |
| Preterm           | 5 (50)   | 5 (50)     |       |
| Gender            |          |            |       |
| Female            | 32 (74.4)| 11 (25.6)  | 0.15  |
| Male              | 6 (100)  | 0 (0)      |       |
| Weight (g)        |          |            |       |
| 1000-1500         | 3 (60)   | 2 (40)     | 0.60  |
| 1500-2500         | 11 (78.5)| 3 (21.5)   |       |
| >2500             | 24 (80)  | 6 (20)     |       |
| Etiology          |          |            |       |
| Sepsis            | 32 (84.2)| 6 (15.8)   | 0.03  |
| Hypovolemia       | 20 (86.9)| 3 (13.1)   | 0.13  |
| Hypoxia           | 11 (64.7)| 6 (35.3)   | 0.11  |
| PDA               | 4 (100)  | 0 (0)      | 0.26  |
| PUV               | 3 (100)  | 0 (0)      | 0.33  |
| Asphyxia          | 2 (100)  | 0 (0)      | 0.43  |
| RVT               | 0 (0)    | 1 (100)    | 0.22  |
| Complications     |          |            |       |
| Convulsion        | 13 (68.4)| 6 (31.6)   | 0.22  |
| Bleeding          | 5 (62.5) | 3 (37.5)   | 0.26  |
| Edema             | 5 (71.4) | 2 (28.6)   | 0.67  |
| Hypertension      | 0 (0)    | 1 (100)    | 0.05  |
| Type of treatment |          |            |       |
| Maintenance       | 22 (70.9)| 9 (29.1)   | 0.14  |
| Dialysis          | 16 (88.8)| 2 (11.2)   |       |
| Neonatal outcome  |          |            |       |
| Death             | 14 (77.7)| 4 (22.3)   | 0.97  |
| Discharge         | 24 (77.4)| 7 (22.6)   |       |

AKI – Acute kidney injury; PDA – Patent ductus arteriosus; PUV – Posterior urethral valve; RVT – Renal venous thrombosis
Table 2: Comparison of AKI newborns based on early outcomes

| Variable          | Early outcomes (%) | P value |
|-------------------|--------------------|---------|
|                   | Discharge | Death   |
| Gestational age   |           |         |
| Term              | 23 (58.9) | 16 (41.1) | 0.21 |
| Preterm           | 8 (80)    | 2 (20)   |     |
| Gender            |           |         |
| Female            | 25 (58.1) | 18 (41.9) | 0.05 |
| Male              | 6 (100)   | 0 (0)    |     |
| Weight (g)        |           |         |
| 1000-1500         | 2 (40)    | 3 (60)   | 0.45 |
| 1500-2500         | 10 (71.4) | 4 (28.6) |     |
| >2500             | 19 (63.3) | 11 (36.7) |     |

Table 3: The role of age, sex, gestational age, weight, BUN, Cr variables on the dialysis in regression equation

| Main variable | OR | Beta | P value |
|---------------|----|------|---------|
| Age           | 0.662 | -0.413 | 0.021 |
| Gender        | 0.006 | -5.162 | 0.519 |
| Gestational age | 0.15 | -1.898 | 0.361 |
| Weight        | 10.368 | 2.339 | 0.116 |
| BUN           | 1.006 | 0.006 | 0.677 |
| Cr            | 3.471 | 1.245 | 0.015 |

in 26 newborns (53.1%). Hydronephrosis in eight newborns (16.3%) and medullary nephrocalcinosis in three newborns (6.1%) were reported.

DISCUSSION

In this study, 49 neonates (1.54%) of 3166 newborns hospitalized in NICU were affected by AKI. The prevalence of AKI in the girls were more than the boys while in other studies, the boys had a higher prevalence of AKI.[6-8] The mean body weight of neonates with AKI was 3510 ± 680 g. In Mathur et al., study[4] the birth weight of <2500 g in AKI group was higher than in healthy neonates. However, in this study, only in 19 cases (38.3%) of newborns birth weight was <2500 g. Thirty-nine (79.5%) of newborns were products of term pregnancy, which is similar to other researches.[8] In this study, the oliguric AKI was more prevalent mainly because more common etiologies of AKI in our patients such as sepsis and dehydration (mainly because of low volume of milk intake and over clothing of neonate). In similar studies, oliguric AKI was also more prevalent.[6,10] The most common cause of AKI in this study was sepsis (77.5%), and after this in order of frequency, hypovolemia (46.9%), hypoxia (34.6%), PDA (8.1%), PUV (6.1%), asphyxia (4%), and RVT (2%). In other studies, prenatal asphyxia has been considered as the most prevalent cause of AKI higher than sepsis which was not consistent with the present observation.[6,8] This may be due to more precise documentation of immediate prenatal, delivery room and postnatal condition of the fetus and newborn in other studies, which has revealed prenatal asphyxia.

In this study, neonatal mortality was 36.7% and sepsis was a main cause of mortality 30.5% of cases. There was a significant relationship neonatal death in this study with hypoxia, asphyxia, need for dialysis and gender, which could be explained as severity of the underlying disease and need for more aggressive treatments. In Gharehbaghi and Peirovifor study, mortality occurred in 20% of the newborns, which was higher in patients with sepsis and ones who needed mechanical ventilation. That was consistent with our study. Furthermore, in a study by Abu-Haweleh,[9] the perinatal asphyxia with the prevalence of 42% was the most common predisposing factor for AKI in neonates and the one most associated with mortality. Thus, it could be said that the leading causes of death in neonates with AKI in the present study was consistent with the most prevalent causes of death in all newborns including infections, prematurity and asphyxia. The mortality rate was found to be higher in patients who underwent PD as a result of worse general conditions and the severity of underlying disease in this group of newborns.

Mathur et al.[4] indicated that AKI was developed in 26.0% of newborns from which 15% were oliguric. The mean gestational age was equal to the number of healthy newborns (36.1 ± 4.1 weeks vs. 36.6 ± 3.5 weeks with P = 0.41), but the number of neonates with a birth weight of <2500 g in the AKI group was higher than that of healthy newborns (86.5% vs. 67.6% with P = 0.008). The association of meningitis, disseminated intravascular coagulation and shock were higher in newborns with AKI and mortality in AKI neonates was higher than the normal subjects (70.2% vs. 25% with P < 0.001). Furthermore, Abu-Haweleh study[9] showed that mortality without dialysis occurred in 45% of neonates. The worst prognosis of patients in this study was associated with asphyxia and the best prognosis with medical treatment.
Csaicsich et al. study also showed that the most common predisposing factor for AKI was sepsis and ischemic events. With conservative management alone, the mortality occurred in 60% of newborns due to multiorgan failure. The highest mortality rate was in oliguric, and patients with birth weight <2500 g. The highest mortality was observed in term neonates, female gender, in birth weight >2500g, oliguric AKI status, and also in dialysis group. In the present research, according to regression results, age was an independent variable of the AKI type (oliguric or nonoliguric). Furthermore, creatinine level and age independent of other variables had a positive and significant effect on dialysis treatment outcome.

In a study on neonates with AKI, high mortality rate was reported, 60% of oliguric AKI patients and up to 86% of patients with concomitant congenital heart diseases and urinary system anomalies died. Among the survivors of oliguric AKI, some causes such as asphyxia, vascular thrombosis, hypotension and toxins were more common, while nonoliguric AKI cases had excellent prognosis. In this study 36.7% died due to AKI of which 14 (77.7%) were oliguric and 4 (22.3%) were nonoliguric. This may be due to comorbid factors such as sepsis in oliguric patients, because 84.4% of sepsis patients were oliguric ($P = 0.03$).

In another study, of 16 AKI neonates, in nine cases the perinatal asphyxia, in four cases renal anomalies and in three cases, congenital heart diseases were risk factors for AKI.

**CONCLUSION**

In this study, sepsis, hypovolemia secondary to dehydration, hypoxia secondary to RDS, PDA, PUV, asphyxia, and RVT were common predisposing factors for AKI in neonates. Among them sepsis, hypoxia secondary to RDS and asphyxia were associated with the highest mortality rate. Therefore, the most common causes of neonatal death in AKI in the present study were consistent with the most common causes of neonatal death including infections, prematurity and asphyxia. Higher mortality rate was associated with term, female, and oliguric AKI states. In the group undergoing PD, higher mortality was possibly due to the worse general condition and the severity of underlying problem such as sepsis. In general, prognosis of AKI in neonates is worse than in adults. Therefore, it is important to prevent AKI by rapid diagnosis of the patients with risk factors and effective treatment of individuals with AKI.

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