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Incidence, Risk Factors and Outcome of Neonatal Acute Kidney Injury: An Observational Study

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ABSTRACT

Introduction

Acute kidney injury (AKI) is common in neonates admitted in neonatal intensive care unit (NICU) and is associated with high death rates and prolong hospital stay. We aimed to determine the incidence, risk factors and outcome of neonatal AKI in a single tertiary center in Nepal.

Methods

This was a prospective observational study of all neonates admitted to NICU between January 2019 to December 2019. Those with AKI were further assessed for risk factors and outcomes. Neonates who survived or stayed less than 72 hours, evidence of congenital renal anomalies, or with incomplete data were excluded. Need of peritoneal dialysis, mortality and length of NICU stay were the outcomes studied among neonates with AKI. Logistic regression models were used for adjustment of covariates and risk analysis were expressed in terms of odds ratio with its 95% confidence interval.

Results

The incidence of AKI was 37.5% (42/112 patients). Compared with neonates without AKI, those with AKI had a lower birth weight (2421±960 vs 1741±1142gram, p<0.001) and a lower gestational age (36.1±7.8 vs. 32.4±3.9 weeks, p<0.001). Sepsis (OR, 4.5; 95% CI, 0.7–30) and nephrotoxic drug exposure (OR, 4; 95% CI, 1.4–7) were significantly associated with increased AKI risk. Mortality was 40% (17/42) among neonates with AKI and 3% (2/70) among those without AKI (p<0.001).

Conclusion

Over one-third of neonates in NICU developed AKI. Prematurity, low birth weight, sepsis and nephrotoxic drug exposure were risk factors for Neonatal AKI. Mortality was almost 50% in neonatal AKI

Keywords
Acute kidney injury, length of hospital stay, mortality, NICU, outcome

INTRODUCTION

Acute kidney injury (AKI) is common in patients in the neonatal intensive care unit (NICU) and associated with poor outcomes. In comparison of older children, the incidence of AKI is higher in newborns where it occurs in 8 to 24% with mortality rates between 10% and 61% along with prolonged hospital stay and increased health care costs.[1-3] Neonates are higher risk of developing AKI because of peculiar physiological characteristics which includes incomplete nephrogenesis, especially in premature neonates, reduced renal blood flow, low glomerular filtration rate and tubular immaturity.

Perinatal asphyxia, neonatal sepsis, prematurity, congestive heart failure, congenital anomalies, therapeutic interventions and certain nephrotoxic drugs are common predisposing risk factors for developing AKI.[4] Although these conditions are the most common reasons for admission in NICU, screening for renal impairment is not often done in resource poor settings like ours. Oliguria is the late manifestation of AKI in neonate. Unlike in older children and adults, renal impairment is usually in advanced stage by the time oliguria appears. Therefore, screening of AKI for all at risk neonates for acute kidney injury may help in early recognition and institution of appropriate measures to prevent further damage.

Over years, there has not been marked reduction in the neonatal mortality in NICU. Many of these neonatal deaths might have been contributed by AKI. There is paucity of data on neonatal AKI in our part of the world; data is scarce to compare the situation with international arena. We therefore carried out this prospective observational study for a period of one year to determine the incidence, risk factors and short-term outcomes of neonatal AKI.

METHODS

This was a single center prospective observational study conducted in NICU of Tribhuvan University Teaching Hospital (TUTH), a referral hospital in Kathmandu, where high risk pregnant women are referred from all over the country. This hospital also serves sick newborns referrred from various parts of the country. All neonates admitted in NICU of TUTH from January 2019 to December 2019 were screened for the study. We excluded neonates who survived for or stayed for less than 72 hrs in NICU, had evidence of congenital renal anomalies, or had incomplete data. Data was considered adequate if at least two measurement of serum creatinine after 72 hours of life or the data of the minimum of one-day record of urine output documented every 6 hours was available.

Written, informed consent was obtained from parents of all admitted neonates in NICU who met the inclusion criteria. Once case is enrolled, we collected demographic data and the information about the potential risk factors for AKI, including the birth weight, gestational age, presence of congenital malformation, blood base excess, Apgar scores at 1 and 5 min, perinatal depression, intraventricular hemorrhage, patent ductus arteriosus (PDA), sepsis and exposure to nephrotoxic medications. For those neonates before 72hrs of life admitted in NICU, we waited till the neonate reach 72hrs of life and serum creatinine was sent within 96 hrs. This was done basically to avoid the effect of maternal serum creatinine (Scr). However, for those neonates who was beyond 96 hrs of life, we sent the serum creatinine on the same day of admission in NICU. If the serum creatinine level was above the reference range (Table 1) for the particular gestational age and post conceptional age, the newborn was suspected to have AKI and was repeated after 48 hours. Serum creatinine was repeated every alternate day till 7 days of life. If neonates stayed in NICU beyond 7 days, serum creatinine were done as when required. We also sent serum creatinine before 72 hours for the newborn with clinical indication. Kinetic–spectrophotometric determination of serum creatinine was conducted using the Jaffe reaction. We collected information on first creatinine and maximum SCr, length of hospital stays (LOS), mortality and need of peritoneal dialysis. Neonates were followed up on daily basis until discharge from NICU. We also recorded the urine output 6 hourly from the day of admission in NICU. For the neonates without urinary catheter, we were weighing diapers and recording urine output 6 hourly. Baby was classified as having AKI based on either serum creatinine criteria, urinary output or both criteria using modified neonatal KDIGO definition of AKI (Table 2).[5]

IBM SPSS Statistics for Windows, Version 20 was

Table 1. Normal serum creatinine concentrations at different ages[2]

Age	Average (mg/dL) [µmol/L]	Range (mg/dL) [µmol/L]
<34 weeks gestational age)		
<2 weeks	0.9 [79.6]	0.7 to 1.4 [61.9 to 123.8]
>2 weeks	0.8 [70.7]	0.7 to 0.9 [61.9 to 79.6]
>34 weeks gestational age)		
<2 weeks	0.5 [44.2]	0.4 to 0.6 [35.4 to 53.0]
>2 weeks	0.4 [35.4]	0.3 to 0.5 [25.6 to 44.2]

Table 2. Neonatal AKI KDIGO Classification[5]

Stage	Serum creatinine (SCr)	Urine output (UOP)
0	No change in SCr or rise < 0.3 mg/dl	≥0.5 ml/kg/hr
1	SCr rise ≥0.3 mg/dl within 48 hrs or SCr rise 1.5-1.9× reference SCra within 7 days	< 0.5 ml/kg/hr for 6 to 12 hrs
2	SCr rise ≥2.0-2.9 × reference SCra	< 0.5 ml/kg/hr for ≥ 12 hrs
3	SCr rise ≥ 3.0 × reference SCra or SCr≥2.5 mg/dlb or receipt of dialysis	<0.3 ml/kg/hr for ≥24 hrs or anuria for ≥ 12 hrs

used for all statistical analyses. Categorical variables were analysed using descriptive statistics such as frequency and percentages. Continuous variables were expressed as mean±standard deviation or median (interquartile range [IQR]), depending upon the normality of distribution. Two group comparisons of continuous variables were performed using Student's t-test, while many group comparisons were performed using ANOVA or the Kruskal-Wallis test for data with normal and non-normal distribution, respectively. The Chi-square test were used for between group comparisons of categorical variables. Step wise logistic regression were used to adjust for potential predictive covariates of AKI, and the results of the risk analysis were expressed in terms of odds ratio (OR) with 95% confidence interval (95% CI). Linear and logistic regression models were used to study the effect of AKI on the LOS, need of peritoneal dialysis and mortality after adjusting for confounders, respectively. Significance level (p value) was set at 0.05.

RESULTS

Out of 114 neonates admitted to our NICU over a 1 year period, 112 patients were screened for AKI. Two neonates were excluded due to the presence of congenital renal anomalies in one neonate and duration of NICU stay less than 72 hours in another neonate.

Table 4. Unadjusted and adjusted risk of AKI for the neonates admitted to the NICU during the 1-year period

Factors	Unadjusted Risk of AKI OR (95 %CI)	Adjusted Risk of AKI OR (95 %CI)
Prematurity	2.66 (1,19)	2.0 (1,17)
Perinatal depression	3.35 (1.8,34.2)	2.3 (1.6,31)
Exposure to nephrotoxic drug	4.2 (1.5, 8.2)	4.0 (1.4,7)
Sepsis	4.7 (0.8,70.1)	4.5 (0.7,30)

Incidence of AKI was 37.5% (42/112): 39 neonates fulfilled serum creatinine criteria only and 3 neonates fulfilled both the Serum Creatinine and Urine Output criteria of the modified neonatal KDIGO definition of AKI. Twenty (46.7%), 14 (33.3%) and 8 (20%) neonates were in AKI stage 1, 2, and 3, respectively as shown in Fig 1. Table 3 summarizes the baseline characteristics of neonates with and without AKI.

Compared to neonates without AKI, those with AKI had a significantly lower gestational age and birth weight. Neonates with AKI exhibited higher incidence of perinatal depression (Table 3). Furthermore, the incidence of sepsis and exposure to nephrotoxic drugs during hospitalization were significantly higher among neonates with AKI than among those without AKI (Table 3).

Using data from the entire cohort, we carried out a risk analysis adjusted for prematurity, perinatal depression, exposure to nephrotoxic drugs, and sepsis. After adjustment, exposure to nephrotoxic drug (OR, 4.0, 95% CI, 1.4–7) and sepsis (OR 4.5, 95%CI, 0.7- 30) were significantly associated with the risk of AKI (Table 4).

The overall mortality rate was 40% (17/42) among neonates with AKI and 3% (2/70) among those without AKI (p<0.001). Not a single AKI patient

Table 3. Baseline characteristics of neonates admitted to the NICU, stratified according to the incidence of AKI

Characteristics	Whole cohort	Non-AKI	AKI	p value
Male sex, n (%)	73 (65%)	50 (72%)	22 (53%)	0.24
Gestational age (wks) - mean±SD	34.7±4.2	36.1±7.8	32.4±3.9	0.005
Birth weight (gm)	2166±1070	2421±960	1741±1142	0.05
Baseline creatinine (mg/dl)	0.59±0.21	0.56±0.23	0.65±0.16	0.21
Highest creatinine (mg/dl)	1.07± 0.97	0.82±1.1	1.48±0.5	0.04
Perinatal depression (%)	42 (37.5%)	11 (16%)	31 (73%)	<0.001
Sepsis, n (%)	84 (75%)	48 (68%)	36 (86%)	<0.001
Exposure to nephrotoxic drug, n (%)	98 (87.5%)	56 (80%)	42 (100%)	<0.001

received renal replacement therapy (RRT). Neonates with AKI had a longer LOS (mean difference, 14.2 days; 95% CI, 5.5–23 days). The median (IQR) LOS was 7 days (1–19) and 13 days (3–39) for neonates without AKI and with AKI, respectively. After adjustment for gestational age, AKI was significantly associated with increased mortality (OR. 5.4; 95% CI, 2–14), but not with the length of hospital stay (LOS) (p=0.13).

DISCUSSION

Incidence of neonatal AKI was 37.5% (42/112): 39 neonates fulfilled serum creatinine criteria only and 3 neonates fulfilled both the serum creatinine and urine output criteria of the modified neonatal KDIGO definition of AKI. This study had shown that 37.5% of the neonates developed AKI which is comparable to the AWAKEN cohort study in which AKI was found in 30% of NICU admitted neonates [6].

The incidence of neonatal AKI in the present study was 37.5 % (42/112) which is comparable to the AWAKEN cohort study in which AKI was found in 30% of NICU admitted neonates

However, study by Shalaby et al had shown more AKI incidence which was 56%.[3] In a study by Timovska et al, Neonatal AKI was seen in only 6.5% (50/770) of newborns admitted in NICU.[7] There may be so many factors such as severity of the disease and the management of neonates admitted in NICU that lead to varying incidence of AKI in different places.

In the present study, 92.8% (39/42) of the neonatal AKI were diagnosed on the basis of serum creatinine criteria only. Low incidence of AKI based on urine output criteria (only 7.2% on both UOP and serum creatinine criteria and none on only UOP criteria) was observed in the current study whereas the study by Bezerra et al had shown 20.5% (64/312) of neonatal AKI were based on UOP criteria only.[8] Slightly higher incidence in Bezerra et al study may be because AKI is considered when UOP <1.5ml/kg/hr for more than 6 hours. However, the criteria devised by Neonatal modified KDIGO classification were followed in this study where AKI is defined as only when UOP <0.5ml/kg/hr for more than 6 hours. The other reason could be the common use of aminoglycoside for treating sepsis in NICU, which might have caused AKI in the form of rising creatinine. With the use of nephrotoxic drug, initially urine output doesnot seem to be decreased especially in premature neonate with immature tubule. Only in the advanced stage, oliguria appears.[6]

Previous several reports had shown that the common risk factors associated with AKI include perinatal depression, sepsis, and nephrotoxic medication exposure.[1,5,9,10] Our study also showed that the predisposing factors for neonatal AKI were sepsis seen in 75%, exposure to nephrotoxic drug in 88% and perinatal depression in 38% of the cases [Table 3]. Some of the other previous reports have shown that sepsis was the leading cause of neonatal AKI and seen in the range of 35 to 80%.[5,11-13] In a prospective study by Doaa Youssef et al, the cause of AKI was found to be pre-renal in 96.3% and intrinsic renal in 3.7% of the cases. The predisposing factors for AKI were sepsis in 63%, respiratory distress syndrome in 55.6%, mechanical ventilation in 51.9%, perinatal asphyxia in 18.5%, dehydration in 14.8%, surgical operation in 11.1%, congenital heart disease in 7.4%, subgaleal hematoma in 3.7%, polycythemia in 3.7% and intra-ventricular hemorrhage in 3.7% of cases.[14]

In the present study, we found out that AKI was significantly common in the most premature neonates which is consistent with the observations by previous studies[4,9,12,15] and also in very low birth weight (VLBW) neonates in concordance with study by Lee et al[16] who reported AKI in 56%. However, in the AWAKEN cohort study and study by Ashkenazi et al, the AKI was also found to be common in older gestational age (34 weeks and more) and higher birth weight neonates which is in contrast to our observation and other previous studies.[6,10] We observed no significant difference in incidence of AKI between male and female (P = 0.24) similar to the study reported by Ashkenazi et al.[10]

We found out that exposure to nephrotoxic drug and sepsis were common in the AKI group. Study by Shalaby et al[3] showed that intraventricular hemorrhage, patent ductus arteriosus, exposure to nephrotoxic drugs were more common in the AKI group. None of our patients had intraventricular hemorrhage and PDA during the study period. Rhone et al.[17] found an inverse linear relationship between birth weight and nephrotoxic medications received per day and reported that neonates with AKI received more nephrotoxic medications per day.

We found out that AKI was associated with higher mortality. In previous studies higher incidence was reported among sicker neonates and among those with risk factors for AKI (e.g., birth weight <1500 g, perinatal asphyxia, or low Apgar scores), those treated with extracorporeal membrane oxygenation, and those requiring cardiac surgery.[5,6] Study by Shabaly et al found that 28.3% of neonates with AKI died.[3] Similarly, Chevalier et al.[18] reported a 25% mortality rate among infants with AKI. Sepsis induced AKI was found to have highest mortaility as shown by the study conducted by Vachvanichsanong et al (65.1% mortality) and Bolat et al (70.2%).[11,12] The AWAKEN study reported mortality of 10% in neonates with AKI, which, however, was much higher than in the neonates without AKI (1%).[6] We

observed overall high mortality rate of 40 % among neonates with AKI compared with only 2.5% among those without AKI.

In our neonates with AKI, none received RRT. In the study by Shalaby et al, two (1.7%) patients with AKI received RRT, which was delivered in the form of acute peritoneal dialysis.[3] Hakam et al[19] reported that RRT was used in less than 1% of neonates with AKI, whereas Lisetal.[20] reported RRT rate of 1–10% in neonates who underwent congenital heart disease repair. Though cardiac surgery is performed in our institute, we have not included neonates who underwent cardiac surgery for our present study. That's why we could not infer how many patients with cardiac surgery develop AKI.

In our study even though length of hospital stay was seen more in premature neonates, AKI was not associated with increased LOS; this finding is in agreement with the previous reports.[3,6] The median (IQR) LOS in our cohort was 7 days (1–19) and 13 days (3–39) for neonates without AKI and with AKI, respectively. Study by Shalaby et al showed that neonates with AKI were hospitalized for a significantly longer period, and LOS was, on average, 14 days longer in the AKI group than in the non-AKI group.[3] Significantly prolonged hospital study was also observed among neonates with AKI in the AWAKEN study and the study by Carmody et al.[6,10]

We had few limitations in our study. First, this was a single-center study conducted in the NICU of tertiary level hospital ; therefore the present findings may not be representative of the situation in other NICUs as patient populations and clinical practices may differ. Second, serum Creatinine alone has some limitations in defining AKI in neonates as there is influence of the mother's creatinine, daily changes in the normal glomerular filtration rate (GFR) after birth, and a wide distribution of the GFR range; therefore, the true incidence of AKI might be even higher than reported.[21] Third, for AKI staging, we used SCr measurements obtained after the first 72hrs of life in order to avoid the effect of maternal creatinine,[16] but this could lead to us missing some AKI patients. Fourth, even though AKI severity is an independent risk factor for poor outcome as shown in previous report,[15] AKI severity versus outcome has not been assessed in this study.

CONCLUSION

The incidence of AKI among all NICU admissions was 37.5%. Sepsis, exposure to nephrotoxic drugs, prematurity and low birth weight were the major risk factors of neonatal AKI. Neonatal AKI had 40% mortality. Therefore, to improve the outcomes of neonatal AKI, it is critical to identify high-risk neonates and perform screening for renal impairment, which facilitates timely intervention.

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CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

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