RESEARCH ARTICLE
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Acute Kidney Injury in Very Preterm Infants: A Cohort Study in A Level III NICU

Güzoğlu et al. Acute Kidney Injury in Very Preterm Neonates

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Abstract
BACKGROUND/AIMS: Acute kidney injury (AKI) is not rare among preterm infants in neonatal intensive care units (NICU). It raises mortality and morbidity in NICU and also chronic kidney disease in the long term. The aim of the study was to define the incidence of clinical characteristics and the course of AKI in very preterm infants.
MATERIALS AND METHODS: A retrospective cohort study was conducted in a level III NICU in a University Hospital, all very preterm infants born in the same hospital during the study period were included in the study. Patient data were taken from the medical records. AKI diagnosis was made using neonatal-modified Kidney Disease Improving Global Outcomes (KDIGO) criteria.
RESULTS: AKI was diagnosed in 20 very preterm infants (42%). The median time of AKI diagnosis was 4.5 days of life (between 2–12 days). While there were 8 infants with AKI when the diagnosis was made based on the serum Cr level being over 1.5, the diagnosis of AKI increased to 20 with the use of KDIGO criteria. Need for resuscitation in the birth room, patent ductus arteriosus, the number of apnea, desaturation episodes, sepsis, hypotension, inotropic support, and sepsis rates were significantly high in the AKI group. Hospitalization day among survivors was longer and mortality was higher in the AKI group than the non-AKI group ($p=0.042$, $p < 0.0001$ respectively).
CONCLUSION: The neonatal KDIGO criteria are beneficial and also informative in diagnosing and staging AKI. Close follow-up of urine output and creatinine levels especially in the first days is essential in very preterm infants,
Keywords: Acute kidney injury; preterm; creatinine

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INTRODUCTION

Acute kidney injury (AKI) is a significant issue in patients who are admitted to neonatal intensive care units (NICU). The AKI prevalence is reported in 40–70% of sick newborns admitted to the NICU (1).

AKI is reported as an independent risk factor for both morbidity and mortality during hospitalization (2). It also may disrupt the function and structure of the kidneys in the long term. While it was assumed that patients with AKI were completely healed, several recent studies have highlighted to be an independent risk factor to develop of chronic kidney disease (3). Therefore, being familiar with the first signs of injury and managing preventive strategies to stop progress is vital.

There are different classification systems to define AKI by measuring serum creatinine levels, glomerular filtration rate and urine output. Recently, neonatal AKI criteria, which is a modified version of Kidney Disease Improving Global Outcomes (KDIGO)-AKI, have been used by clinicians in NICUs (4, 5).

This study aimed to define the incidence of clinical characteristics and the course of AKI in very preterm in our NICU. We used neonatal-modified KDIGO criteria to define and stage neonatal AKI (Table 1).

MATERIALS AND METHODS

This retrospective cohort study was conducted with very preterm infants who were admitted to a level III NICU in a University Hospital. The study was conducted from December 2015 to December 2016. All very preterm infants (gestational age less than 32 weeks) who were followed from the first hours of life were included in the study. Patients with multiple congenital anomalies, congenital heart disease except PDA, kidney, and urinary tract malformations were excluded. Infants who survived less than 48 hours and infants who were accepted after the first day of life were also excluded.

Infants diagnosed with AKI during their follow-up were defined as AKI-group. The non-AKI group consisted of very preterm infants without developing AKI during the same period. Maternal characteristics including age, preeclampsia, hypertension, diabetes, urinary tract infection, HELLP syndrome, and patients' clinical characteristics including delivery type, gender, gestational age, Apgar scores at 5 min, birth weight, respiratory support, daily weight and fluid volume, urine output, medications, laboratory results, presence of hemodynamically significant patent ductus arteriosus (PDA), sepsis, duration of hospital stay, and mortality were obtained from the medical records.

AKI diagnosis and staging were defined depending on the neonatal KDIGO criteria, shown in Table 1. The KDIGO stage was determined by considering the values of either the lowest urine output or the highest serum creatinine level in the follow-up of the patients. The local ethics committee approved the study.

Statistical Analysis

Statistical analyses were studied by IBM SPSS Statistics V22.0. Demographic characteristics of patients were compared between the AKI and non-AKI groups. For the evaluation of the study values such as median, minimum, and maximum we used descriptive statistical methods. Chi-squared tests were used to compare the qualitative data. Mann-Whitney U test was used to compare differences in quantitative variables with non-normally distributed for two groups.

RESULTS

During the study period, 52 infants born very prematurely were admitted to the NICU within the first hours of life. After excluding neonates based on the exclusion criteria, 44 were included in the study. AKI was diagnosed in 20 with an estimated prevalence of 42% in the study population according to modified KDİGO criteria. Of the 20 patients diagnosed with AKI; 11 were stage 1 (55%), 6 were stage 2 (30%), and 3 were grade 3 stage (15%). The median time of AKI diagnosis was 4.5 days of life (between 2–12 days).

There was a significant difference in serum creatinine (Cr) levels between patients with AKI (1.42±0.6) and the non-AKI (0.63±0.1) group ($p<0.0001$). Although serum Cr level higher than 1.5 mg/dl, 8 preterm infants were diagnosed as AKI, which increased to 20 with KDIGO criteria. 2 patient was diagnosed with only urine output criteria. Mean serum creatinine level was 1.2±0.3 in stage 1, 1.19±0.45 in stage 2 and 2.5±0.6 in stage 3 infants.

Gestational week was significantly lower ($p=0.011$) and the male ratio was higher in the AKI group (0.01). Median birth weight was lower in the AKI group; however, there was not statistically significant difference. Maternal characteristics of the AKI group and demographic characteristics of both groups are shown in Table 2 and 3.

In the AKI group, the need for resuscitation in the birth room was higher. No difference noticed between the groups in terms of initial urine output and fluid loads. However, there was a significant difference in the number of apnea, desaturation episodes, sepsis, hypotension, inotropic support, and sepsis (Table 4).

Length of stay among survivors was significantly longer in the AKI group (median: 47 days) than in the non-AKI group (median: 28 days) $p=0.042$ (Table 4).

In the AKI group mortality was significantly high (65 % vs 2%, $p < 0.0001$), with an OR of 3.5 (1.8-7.0).

DISCUSSION

Acute kidney injury is common in preterm babies admitted to the NICU as reported in the literature. Carmody et al. showed that the AKI incidence in very low birth weight infants was 40 % (6). Weintraub et al. reported the AKI incidence as 30.3% in less than 30 gestational weeks (7). In a prospective study from Saudi Arabia AKI incidence was 56% in infants who were admitted to level- 2 and 3 NICUs (8). In a multicentric study, which include 24 NICUs, the incidence of AKI was 29.9%, and the rate increased to 47.9% for infants less than 29 gestational weeks (9). In our study we found that AKI incidence in very preterm infants was 45.4 %

Although there was no difference in terms of gender in the studies (6, 9, 10), male gender was significantly higher in the AKI group in our study. In our study, the gestational week was significantly lower in infants with AKI. The study by Higorani et al showed an inverse relation between severe AKI incidence and the gestational age in an extremely low gestational age

neonate group. Additionally, they reported that mean birthweight was lower in newborns with severe AKI than with none/stage 1 AKI (2).
The AWAKEN study that examined the incidence and outcomes of AKI in newborns found AKI diagnoses most often during the first week after birth (9). The median day of AKI diagnosis was 4.5 (2-12 days) in this study. Like the previous studies, stage 1 frequency was higher than other stages, additionally, stage 2 and 3 AKI is related to higher mortality (11, 12).
The mean serum creatinine level was higher than 1.5 mg/dl only in stage 3. Therefore, diagnosis and early prevention strategies are very crucial in the early period that is the creatinine levels have not yet increased in most of them. Gomez et al. showed that while most patients' kidney function healed in the first stage, just half of the patients' kidney function healed in the severe stage (12).
It is well known that the significant cause of neonatal AKI is asphyxia. In our study, there were 6 patients within the AKI group. Alaro et al reported that full-term neonates with hypoxic ischemic encephalopathy had a 15 times higher risk of AKI (13). Kaur et al. examined the incidence of AKI among ≥34 gestational week neonates with birth asphyxia. They reported that the incidence was 41.7% (14).
In our study overall, preterm with AKI had more inotropic treatment than those without AKI. Additionally, patent ductus arteriosus, sepsis, apne, and desaturation attacks were more commonly in the AKI group. Moreover, vancomycin usage was higher in the AKI group, however; all patients had the treatment after the AKI attack. Different studies reported that gestational age, outborn delivery, the need for high mean airway pressure, non-steroidal anti-inflammatory treatment for patent ductus arteriosus, hypotension, necrotizing enterocolitis, sepsis, hyperbilirubinemia, inborn errors of metabolism, and need of surgery were associated with AKI (7, 10, 15).
Day of hospitalization in NICU among survivors was longer in the AKI group than the non-AKI group and the mortality rate also was higher in the AKI group in the study (OR = 3.5, 95% Cl 1.8-7.0). It was described that neonatal AKI had a more than 4 fold higher risk of death and was related with longer hospitalization day (8.8 days), 4 fold higher risk of death, and increased length of stay (11.7 days) in VLBW infants (6, 9). Charlton reported that neonatal having AKI in the first postnatal week is associated with 2.8 fold higher risk of death and 7.3 days longer LOS in the hospital (15). Koralkar et al indicated that AKI was strongly associated with mortality in a prospective in VLBW infants (16).
AKI is not rare among patients in the NICU, because of the short and long-term outcomes of the patients and the significance of early recognition, different neonatal AKI definitions are suggested. However, a study with neonatologists and pediatricians from India, an online survey was conducted. More than half of the participants were not familiar with the standard neonatal AKI criteria. Additionally, most respondents were unaware of the risk of AKI due to prematurity (1).

Study Limitations

Although the small number of cases and being a single center are limitations of our study, the fact that the results of the study are very similar when compared with the literature emphasizes the importance of early diagnosis of AKI in the neonatal period.

CONCLUSION

In conclusion, delays in diagnosis and inappropriate management of AKI are associated with adverse outcomes, longer hospitalization days, and high mortality. For the early diagnosis, the first step should be awareness and close monitoring. The neonatal-modified KDIGO criteria are

very beneficial and also informative in follow-up. For very preterm infants, close follow-up of urine output and creatinine levels especially in the first days is highly recommended.

MAIN POINTS

- AKI is a common issue in premature patients who are admitted to neonatal intensive care unit.
- AKI is associated with adverse outcomes during hospitalization, so awareness and close monitoring are essential.
- The neonatal-modified KDIGO criteria are beneficial for the early diagnosis of AKI.

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Table1. Modified Neonatal Acute Kidney Injury Criteria[5]

	Serum creatinine	**Urine output**
Stage 1	≥ 0.3 rise within 48 h or ≥ 1.5–1.9 × rise from baseline (previous lowest value) within 7 days	≤ 1 ml/kg/h for 24 h
Stage 2	2.0–2.9 times baseline	≤ 0.5 ml/kg/h for 24 h
Stage 3	≥ 3 × rise from baseline or serum creatinine ≥ 2.5 mg/dl or renal replacement therapy initiation	≤ 0.3 ml/kg/h for 24 h

Table 2. Demographic characteristic

Variables, *med(min-max)*	**AKI (n=20)**	**Non-AKI (n=24)**	**P**
Mother's age	27 (16-39)	24 (17-37)	0,795
Delivery Type (C/S)	16(84)	24(96)	0,17
Gestational week median(min-max)	28(24-32)	30(25-32)	0,011*
Birth weight	1205(580-1890)	1435(600-1860)	0.141
5. min Apgar score	8(4-10)	8 (6-10)	0,044*
Male gender	16(80)	10(42)	0,01*

AKI, Acute Kidney Injury; C/S, Cesarean birth; *significant

Table 3. Maternal characteristics of patients with AKI		
Variables, *n (%)*	**AKI (n=20)**	**Non-AKI (n=24)**
Gestational hypertension or Preeclampsia	4 (21)	2 (8)
Urinary tract infection	5 (26)	4 (16)
Hellp Syndrome	-	3 (12)
Placental abruption	2 (10)	2 (8)
Hiperemezesis gravidarum		- 1 (4)

Table 4. Clinical conditions and comorbidities in the newborns			
Variables, *n(%)*	**AKI (n=20)**	**Non-AKI (n=24)**	**p**
Intubated in the delivery room	1(4)	13(65)	0,000*
Respiratory distress syndrome	20(83)	16(80)	0,539
Patent ductus arteriosus	11(44)	15(79)	0,02*
Birth asphyxia	0	6(32)	0,002*
Desaturation attacks	9(38)	17(85)	0,002*
Apne attacks	9(38)	19(95)	0,000*
Hypotension-Shock	4(17)	16(80)	0,000*
Sepsis	8(33)	19(95)	0,000*
Invaziv mechanical ventilation	5 (21%)	7 (35%)	0,29
Inotropes	5 (21%)	90 (72%)	0,000*
Nephrotoxic medicine			
NSAID	5 (21)	4(21)	0,622
Vancomycin	4(17)	13(68)	0,001*
Furosemide	1(4)	13(65)	0,000*
Amphotericin B	0	2(10)	0,20
Length of stay	28 (7- 86)	47 (17-136)	0,042*
AKI, Acute Kidney Injury; NSAID, Non-steroidal anti-inflammatory drugs; *significant			