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

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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 NICUs and also chronic kidney disease in the long term. The aim of this 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 this study. Patient data were taken from the medical records. AKI diagnosis was made using the 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 creatinine (Cr) level being over 1.5, the diagnosis of AKI increased to 20 with the use of the KDIGO criteria. Need for resuscitation in the birth room, patent ductus arteriosus, the number of cases of apnea, desaturation episodes, sepsis, hypotension, inotropic support, and sepsis rates were significantly higher in the AKI group. Days hospitalized among survivors were longer and mortality was higher in the AKI group than in 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 Cr levels especially in the first days is essential in very preterm infants.

Keywords: Acute kidney injury, preterm, creatinine

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 to be 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 may also 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 it to be an independent risk factor in the development of chronic kidney disease.[3] Therefore, being familiar with the first signs of injury and managing preventive strategies in order to stop its progress is vital.

There are different classification systems used to define AKI by measuring serum creatinine (Cr) levels, glomerular filtration rates 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]

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This study aimed to define the incidence of clinical characteristics and the course of AKI in very preterm babies in our NICU. We used the 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. This study was conducted between December, 2015 and December, 2016. All very preterm infants (gestational age less than 32 weeks) who were followed from the first hours of life were included in this study. Patients with multiple congenital anomalies, congenital heart disease except for patent ductus arteriosus (PDA), kidney, and urinary tract malformations were excluded. Those infants who survived less than 48 hours and those who were accepted after their first day of life were also excluded.

Infants diagnosed with AKI during their follow-up were defined as the AKI-group. The non-AKI group consisted of very preterm infants who did not develop AKI during the same period. Maternal characteristics including age, preeclampsia, hypertension, diabetes, urinary tract infection, HELLP syndrome, and the 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, the presence of hemodynamically significant PDA, sepsis, duration of hospital stay, and mortality were obtained from the medical records.

AKI diagnosis and staging were determined based on the neonatal KDIGO criteria as shown in Table 1. The KDIGO stage was determined by considering the values of either the lowest urine output or the highest serum Cr level in the follow-up of the patients. This study was approved by the Ethics Committee of Malatya Turgut Özal University Non-interventional Clinical Research Ethics Committee (approval number: 2022/128, date: 09.08.2022).

Statistical Analysis

Statistical analyses were carried out by IBM SPSS Statistics V22.0. The demographic characteristics of the patients were compared between the AKI and non-AKI groups. For the evaluation of the study values such as medians, minimums, and maximums, we used descriptive statistical methods. The chi-square test was used to compare qualitative data. The Mann-Whitney U test was used to compare differences in quantitative variables with non-normal distributions for two groups.

RESULTS

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

There was a significant difference in serum Cr levels between those patients with AKI (1.42±0.6) and the non-AKI (0.63±0.1) group ($p<0.0001$). With serum Cr levels higher than 1.5 mg/dL, 8 preterm infants were diagnosed as AKI, which increased to 20 when using the KDIGO criteria. Two patients were diagnosed based only on their urine output criteria. The mean serum Cr 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.

The gestational week was significantly lower ($p=0.011$) and the male ratio was higher in the AKI group ($p=0.01$). The median birth weight was lower in the AKI group, however, there was no statistically significant difference. The maternal characteristics of the AKI group and the demographic characteristics of both groups are shown in Tables 2, 3.

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

The 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).

Table 1. 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) n (%)	16 (84)	24 (96)	0.17
Gestational week	28 (24-32)	30 (25-32)	0.011*
Birth weight	1,205 (580-1,890)	1,435 (600-1,860)	0.141
5-min Apgar score	8 (4-10)	8 (6-10)	0.044*
Male gender n (%)	16 (80)	10 (42)	0.01*

AKI: Acute kidney injury, C/S: Cesarean birth, *Statistically significant, min.: Minimum, max.: Maximum.

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)
Hyperemesis gravidarum	-	1 (4)

AKI: Acute kidney injury.

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*
Apnea attacks	9 (38)	19 (95)	0.000*
Hypotension-shock	4 (17)	16 (80)	0.000*
Sepsis	8 (33)	19 (95)	0.000*
Invasive 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, *Statistically significant.

The AKI group mortality was significantly higher (65% vs. 2%, p<0.0001), with an odds ratio (OR) of 3.5 (1.8-7.0).

DISCUSSION

AKI is common in preterm babies admitted to the NICU as reported in the literature. Carmody et al.[6] showed that the AKI incidence in very low birth weight infants was 40%. Weintraub et al.[7] reported an AKI incidence of 30.3% at less than 30 gestational weeks. 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 multi-center study, which included 24 NICUs, the incidence of AKI was 29.9%, and this rate increased to 47.9% for those infants born at less than 29 gestational weeks.[9] In our study, we found that the AKI incidence in very preterm infants was 45.4%.

Although there was no difference in terms of gender in some 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 those infants with AKI. The study by Hingorani et al.[2] 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 those newborns with severe AKI than in those with none/stage 1 AKI.

The AWAKEN study which 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. Similar to the previous studies, stage 1 frequency was higher than the other stages, and stage 2 and 3 AKI were related to higher mortality.[11,12]

The mean serum Cr 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 when the Cr levels have not yet increased in most cases. Pantoja-Gómez et al.[12] showed that while most patients' kidney function healed in the first stage, just half of the patients' kidney function healed in the severe stage.

It is well known that a significant cause of neonatal AKI is asphyxia. In our study, there were 6 patients within the AKI group. Alaro et al.[13] reported that full-term neonates with hypoxic ischemic encephalopathy had a 15 times higher risk of AKI. Kaur et al.[14] examined the incidence of AKI among ≥34 gestational week neonates with birth asphyxia. They reported that the incidence was 41.7%.

In our study overall, preterm infants with AKI had more inotropic treatment than those without AKI. Additionally, patent ductus arteriosus, sepsis, apnea, and desaturation attacks were more commonly seen in the AKI group. Moreover, vancomycin usage was higher in the AKI group. However, all patients had treatment after their AKI attack. Different studies reported that gestational age, out-born 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 the need of surgery were associated with AKI.[7,10,15,16]

The number of days of hospitalization in the NICU among the survivors was longer in the AKI group than in the non-AKI group and the mortality rate also was higher in the AKI group in this study (OR: 3.5, 95% confidence interval: 1.8-7.0). It has been stated that neonatal AKI has a more than 4-fold higher risk of death and was related with longer hospitalization (8.8 days), as well as a 4-fold higher risk of death, and increased length of stay (11.7 days) in very low birth weight (VLBW) infants.[6,9] Charlton reported that neonatal infants having AKI in the first postnatal week is associated with a 2.8-fold higher risk of death and 7.3 days longer LOS in hospital.[15] Koralkar et al.[17] indicated that AKI was strongly associated with mortality in a prospective study on VLBW infants.

AKI is not rare among patients in NICUs. Due to its short and long-term outcomes and the significance of early recognition, different neonatal AKI definitions have been suggested. However, in a study with neonatologists and pediatricians from India using an online survey, 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

The fact that this study only examined a small number of cases and was based on a single center are the limitations of this study. However, the fact that the results of this study are very similar when compared with the literature emphasizes the importance of the 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 hospitalizations, and higher 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 the follow-up. For very preterm infants, close follow-up of urine output and Cr 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 units.

- 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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ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Malatya Turgut Özal University Non-interventional Clinical Research Ethics Committee (approval number: 2022/128, date: 09.08.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ü.A.T., A.B., D.A., Concept: N.G., B.Ç.A., D.A., Design: N.G., B.Ç.A., D.A., Data Collection and/or Processing: Ü.A.T., A.B., Analysis and/or Interpretation: N.G., Ü.A.T., A.B., Literature Search: N.G., Writing: N.G., B.Ç.A.

DISCLOSURES

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