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Original Article

Assessment of Kidney Injury Molecule-1 in Acute Kidney Injury in the Neonatal Intensive Care Unit: A Study in Northeast Iran from 2019 to 2020

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ABSTRACT

Background: Drugs cause approximately 20%-40% of acute kidney injuries (AKI). Amikacin (AMK) is one of the common medications used as empiric therapy for severe infections, such as sepsis in neonates. One of the newly recommended biomarkers in AKI is Kidney Injury Molecule-1 (KIM-1). In this study, we evaluated the use of KIM-1 for diagnosing tubular injury in neonates treated with Amikacin in the neonatal intensive care unit (NICU) of our educational hospital in Gorgan, Iran.

Methods: This cross-sectional descriptive study was conducted at the NICU of the two educational hospitals affiliated to the Golestan University of Medical Sciences, Gorgan, Iran. There were two groups of patients, namely neonates treated with Amikacin plus Ampicillin (group A; n=45) and neonates treated with Ampicillin plus Cefotaxime (group B; n=45). Demographic characteristics were recorded. Blood and urine samples were collected in both groups. The urinary secretion of KIM-1 was determined using an ELISA kit.

Results: The total number of patients in both groups was 45, 26 (57.8%) of whom were male, and 19 (42.2%) cases were female. The mean age was obtained at 5.25±1.47 days in group A and 5.15±1.5 days in group B. None of our patients had AKI. There was no difference between leukocyte count and platelets on the first and seventh day. There was a significant difference among K, Na, urine specific gravity, C-reactive protein, Cr, and BUN on the seventh day, compared to the first day. The difference between urinary levels of KIM-1 in the two groups was not statistically significant.

Conclusion: We have not found a significant relationship between urinary KIM-1 and AKI in our patients.

Keywords: Acute kidney injuries, Neonatal intensive care unit, Neonate

Introduction

Many medications and their metabolites are excreted in the urine and can have side effects, such as nephrotoxicity, because of the high concentration achieved in the kidney (1). Drugs cause approximately 20%-40% of acute kidney injuries (AKI). AKI is defined as an increase in serum creatinine (Scr) by ≥0.3 mg/dL within 48 h, ≥50% increase in Scr within 7 days, or urine output < 0.5 mL/kg/h for 6 h (1, 2).

The two common antimicrobials that cause AKI are aminoglycosides and beta-lactams. Aminoglycosides cause a dose-related reduction in kidney function in 10%-20% of patients. Most of their elimination is through urinary excretion. Proximal tubule toxicity is the most common cause of aminoglycoside-caused renal toxicity. The

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most nephrotoxic agents in this group are Gentamicin, Tobramycin, and Amikacin (AMK). AMK is one of the common medications used as empiric therapy for severe infections, such as sepsis, in neonates (1-3).

The most common biomarker for assessing kidney function or glomerular filtration rate (GFR) is Scr. Scr variability is related to different factors, including birth weight, gestational age, and postnatal age. For considering Scr as a marker of kidney function in neonates, such issues as renal tubular transport, hydration, muscle mass, and measurement methods should be considered. Because of the limitations of using Scr in AKI, new methods are being investigated.

One of the newly recommended biomarkers in AKI is Kidney Injury Molecule-1 (KIM-1) (1). KIM-1 was introduced firstly by Ichimura et al. as a marker that sheds urine after acute kidney damage and is considered a marker of renal tubular injury. They also identified that KIM-1 overexpression is a marker for the long-term prognosis of chronic kidney diseases. KIM-1 is a type 1 transmembrane protein, with an immunoglobulin and mucin domain. Kidney expresses KIM-1 in the acute injury resulting from ischemia, hypoxia, toxicity, or some renal tubular interstitial, and polycystic kidney disease making it a reasonable marker in the diagnosis of AKI (1-4). KIM-1 is a novel way of understanding AKI that is not yet an approved method in neonatal AKI. In this study, we evaluated the use of KIM-1 for diagnosing tubular injury in neonates treated with AK in the Neonatal Intensive Care Unit (NICU) of our educational hospital in Gorgan, Iran.

Methods

This descriptive study was conducted at the NICU of the two educational hospitals affiliated to the Golestan University of Medical Sciences, Gorgan, Iran.

We included neonates with suspected or confirmed sepsis admitted to our hospital over a year (from February 2019 to February 2020). There were two groups of patients, namely neonates treated with Amikacin plus Ampicillin (group A; n=45) and neonates treated with Ampicillin plus Cefotaxime (group B; n=45).

The inclusion criteria were 1) neonates with sepsis symptoms, such as poor feeding, tachypnea, spasticity, and hypotension who were confirmed by laboratory data, 2) neonates admitted to the NICU for less than 24 hours or diagnosed at the admission, 3) neonates without kidney disease (hydronephrosis/anatomical disorders/urinary tract infection) and asphyxia, and 4) no history of taking Amikacin at the first day of birth.

Demographic characteristics (gestational age, weight, gender, duration of admission, and mortality) were collected. Heart rate and mean arterial pressure, mechanical ventilation, primary creatinine (baseline), and serum urea were also recorded.

Associated conditions were classified as asphyxia, preeclampsia (>37 weeks), congenital diseases, and others (e.g., gastrointestinal disorders, shock, intracranial hemorrhage, and respiratory failure).

Blood and urine samples were collected in both groups. Fresh urine samples were collected twice (on the first and seventh days). The samples were stored at -80 °C until they were analyzed. The urinary secretion of KIM-1 was determined using an ELISA kit. The cut-off value for kidney failure was 0.35 ng/mg UCr.

AKI was diagnosed if a change in Scr (0.3 mg/L or a 1.5-fold increase) occurring 48 h after birth or a decrease in urinary output (<1 mg/kg body weight per hour [in 6 h]), which meets the AKI network criteria (5).

Statistical Analysis

The latest version of SPSS software was used for statistical analysis. Covariance analysis, chi-square analysis, independent t-test, or equivalent nonparametric tests were used to compare the mean parameters in the groups. The normality scale was measured by the Shapiro-Wilk test. All the variables were compared using the Mann-Whitney U test, except for Polymorphonuclear counts which were compared utilizing an independent t-test. A P-value of less than 0.05 was considered statistically significant, and the results were indicated as mean±SD.

Ethical approval

The study protocol was approved by the Ethics Committee of GOUMS (IR.GOUMS.REC.1399.173), and all the parents filled out the informed written consent. The patients' information was kept confidential.

Results

The total number of patients in both groups was 45, 26 (57.8%) of whom were male and 19 (42.2%) cases were female. In both groups, male to female ratio was 1.36, and it was not statistically significant. The mean age was

Table 1. Basic characteristics of the neonates admitted to the NICU due to sepsis (clinical or suspected)

Variable		Amikacin and Ampicillin Group	Cefotaxime and Ampicillin Group
Weight (gr), mean±SD		2856.67±401.21	2900.56±519.0
Length (cm), mean±SD		48.74±0.23	49.64±1.31
BMI (kg/m^2), mean±SD		12.74±0.16	13.00±1.60
Gender	Male	26(57.8%)	26(57.8%)
	Female	19(42.2%)	19(42.2%)
Age(days), mean±SD		5.25±1.47	5.15±1.5

5.25±1.47 days in group A and 5.15±1.5 days in group B. In group A, 31 (68.9%) neonates had clinical sepsis, 12 (26.7%) patients were suspected cases, and 2 (4.4%) newborns had definite sepsis. In group B, there were 18 (40%) cases of clinical sepsis, 9 (20%) neonates were suspected cases, and 18 (40%) newborns had definite sepsis.

It is worth mentioning that none of our patients had AKI.

The characteristics of the patients are shown in Table 1.

There was no difference between leukocyte count and platelets on the first and seventh day.

The differences between mean laboratory findings on the seventh day are shown in Table 2.

There was a significant difference among K, Na, urine specific gravity (SG), C-reactive protein (CRP), Cr, and BUN on the seventh day, compared to the first day. The difference between the urinary levels of KIM-1 in the two groups was not statistically significant, but the mean level of this marker was lower in the Amikacin group (group A).

Table 2. The differences among laboratory findings of neonates with sepsis admitted to the NICU in two groups on seventh days

Variable	Amikacin and Ampicillin Group, mean±SD	Cefotaxime and Ampicillin Group, mean±SD	P-value
Urea(BUN), mg/dl	16.13±9.78	7.73±2.15	0.00
Creatinine, mg/dl	0.63±0.17	0.52±0.067	0.00
C-reactive protein, mg/dl	1.66±3.65	3.98±3.75	0.004
Urine SG	1008.29±2.99	1009.89±2.90	0.012
Sodium (Na), mEq/l	138.44±3.52	140.58±4.351	0.012
Potassium (K), mEq/l	4.91±0.53	4.55±0.65	0.005
KIM-1, pg/ml	2.73 ±0.78	3.07±0.95	0.07

Discussion

In this study, we used a new biomarker named KIM-1 in urine samples for the diagnosis of AKI in neonates. Our results have shown no statistical difference between the two groups considering KIM-1 in urine samples.

Sridharan et al. found that KIM-1 levels can reflect renal function in critically-ill neonates. They included 70 neonates who were receiving one or more potential nephrotoxic drugs (6), and it was also similar to the results of some other studies, such as Correa et al. (7); however, our findings were not the same and the mean level of KIM-1 was lower in group A although it was not significant.

Neonatal sepsis is a common condition in the NICU, especially in preterm neonates. Most of the medications we are using in the treatment of neonatal sepsis have serious side effects, such as nephrotoxicity in addition to hearing loss, as we showed in a previous study in our academic hospital (8, 9). It is reasonable to find fewer toxic agents for the treatment. Many studies targeted this issue; however, there are still challenges in this topic. Out of 90 patients, who were treated with intravenous antibiotics, none of them had developed AKI.

There was a significant difference among laboratory parameters, including sodium, potassium, CRP, urine SG, urea, and creatinine on the seventh day of treatment. The BUN and creatinine levels were higher in the Amikacin group, compared to the Cefotaxime group. On the other hand, the levels of other measures were higher in the Cefotaxime group. Alinejad et al. in 2018 compared the nephrotoxic effects of two antibiotics in 80 neonates with sepsis and reported no significant differences among GFR, urea, and Scr after treatment with Amikacin or Gentamicin (10). However, in another study, Eslami et al. reported 17 neonates treated with Amikacin that had changes in Scr levels after treatment (11) that were compatible with our study.

Limitations of the Study

Our study used KIM-1 in AKI among neonates that have not been evaluated before; however, we did not have serum Amikacin level, fraction excretion of sodium, urinary sediment, and sodium. It is recommended that these variables be assessed in future studies.

Conclusion

We have not found a significant relationship between urinary KIM-1 and AKI in our patients. However, it seems that the mean of KIM-1 levels is lower in patients who received Amikacin and Ampicillin, compared to the other group. Considering the value of this biomarker for predicting the risk of AKI, based on the previous studies, we need to investigate it more in the future.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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