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Original Article

Serum KIM-1 and Cystatin Levels as the Predictors of Acute Kidney Injury in Asphyxiated Neonates

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ABSTRACT

Background: Asphyxia may lead to serious complications, among which acute kidney injury (AKI) is the most common. Early diagnosis of AKI can help prevent impaired acid-base, fluid, and electrolyte balance that may lead to life-threatening complications. This study aimed to evaluate the effect of kidney injury molecule-1 (KIM-1) and cystatin-C in the early diagnosis of AKI among asphyxiated neonates.

Methods: This case-control study was conducted on 45 asphyxiated neonates, 24 of whom were in the control group and 23 cases were in the case group. Creatinine (Cr), KIM-1, and cystatin-C were measured for participants within 8 h and 4 days after birth and compared between case and control groups.

Results: The mean level of Cr-Standardized KIM-1 measured within 8 h and 4 days after birth was significantly higher in the case group, compared to the control group (P-value<0.05). The mean level of Cr-Standardized cysteine, only 4 days after birth, was significantly higher in the case group, compared to the control group (P-value<0.05). A receiver operating characteristic (ROC) curve analysis demonstrated that between the two biomarkers with two measurements, the KIM-1 Cr-Standardized within 4 days had the highest area under the curve (AUC) (0.751, 95% CI: 0.597-0.905). Moreover, the results of ROC curve analysis showed that Cr-Standardized KIM-1 within 4 days after birth with a critical value of >0.67 ng/ml allowed to predict kidney failure in newborns with 57.1¬% sensitivity and 86.4¬% specificity.

Conclusion: The findings of the present study show that high-specificity KIM-1 is a good biomarker for the early detection of acute renal failure in asphyxiated infants; however, similar expectations cannot exist with regards to cystatin-C for at least the first 8 h after birth.

Keywords: Acute kidney injury, Asphyxia, Cystatin-C, Kidney injury molecule-1

Introduction

Perinatal asphyxia refers to the lack of flow or gas exchange to or from the fetus right before, during, or after the process of birth. Perinatal asphyxia can lead to significant systemic and neurological problems because of the reduction of blood flow and/or oxygen to a fetus or infant during the process of birth. The cease or reduction of placental (perinatal) or pulmonary (immediate post-natal) gas exchange will result in partial (hypoxia) or complete (anoxia) loss of oxygen in vital and biotic organs. Therefore, progressive hypoxemia and hypercapnia will happen (1,2).

The approximation of perinatal asphyxia occurrence differs across the world. In developed countries, the occurrence of severe perinatal asphyxia (i.e., those causing death or severe neurological impairment) is about 1/1000 live births, while in developing countries, it is much more common, about 5-10/1000 live births (3,4). However, this rate of occurrence seems an

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underestimation of the real number of perinatal asphyxia in developing countries (5). Intensive asphyxia and ischemia lead to the occurrence of reperfusion in various organs, including the heart, brain, and adrenals, which can injure organs, such as the skin, kidneys, and gastrointestinal tract (6,7). The kidneys are the most injured organs in ischemia (7). In adults and children, acute kidney injury (AKI) can be measured simply; however, its measurement in newborns is very complex (8). AKI refers to an acute decrease of kidney function, leading to uremia, modified fluid balance, and disturbed electrolyte homeostasis (8) In severely ill neonates, AKI is comparatively usual and happens mostly in the first days of life, then it leads to hypovolemia, hypotension, ischemia, and less frequently, to primary kidney illness. Traditionally, AKI has been described as the growth of serum creatinine (Cr) above 1.5 mg/dL (132 µmol/L). AKI is often observed in neonates, and about 8%-24% were observed among those in the neonatal intensive care units (NICU). AKI leads to higher death rates and more risks of the development of chronic kidney illness. Furthermore, it is traditionally diagnosed by measuring blood urea nitrogen and Cr, although these methods are not sensitive and specific to AKI (9) It has been observed that some found proteins from serum and urine are the signs of AKI, even prior to the increase of blood urea nitrogen and Cr (10). The most important kinds of these proteins are neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 (KIM-1), cystatin-C, interleukin-18, and liver-type fatty acid-binding protein. KIM-1 is an adhesion molecule observed in mucous cells. A small amount of KIM-1 and its messenger ribonucleic acid is acceptable in a normal kidney; however, significant increases in their concentration can be regarded as a sign of ischemic kidney (11,12). It is mentioned that KIM-1 plays a central role in the procedure of mucous regeneration and removing dead cells from the tubular lumen through phagocytosis.

All cells with a nucleus include cystatin-C. This protein is easily filtered in the glomerulus, entirely reabsorbed in the proximal tubules, and kept in the renal tubules. It has been observed that in patients suffering from AKI, cystatin-C levels increase 1-2 days earlier than the rise of serum Cr levels, and that cystatin-C is a better indicator of glomerular filtration pace (13,14).

In spite of the improvements in perinatal care, perinatal asphyxia is still one of the critical issues which can lead to death and disease at birth. Asphyxia leads to the malfunction of different body organs and more specifically, renal failure. Primary diagnosis of AKI in the perinatal group may lead to better treatment results. Due to the limitations of Cr in renal failure diagnosis and the significance of early detection of renal failure in curing patients, the biomarkers of KIM-1 and cystatin-C were used in the present study. Therefore, the present study has been conducted to evaluate the biomarkers of KIM-1 and cystatin-C, and compare them with Cr in infants suffering from asphyxia caused by renal failure.

Methods

Study design

This case-control study was performed at the NICUs of Alzahra and Shahid Beheshti Hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, from April 2016 to September 2018.

Study population

The study population included all neonates with asphyxia who were admitted to the NICUs of Alzahra and Shahid Beheshti Hospitals affiliated to Isfahan University of Medical Sciences Isfahan, Iran.

Inclusion and exclusion criteria

The inclusion criteria were infants with: 1) gestational age of 34 weeks or older, 2) perinatal asphyxia 31, 3) acute renal failure (ARF), and 4) parental consent to participate in the study. On the other hand, neonates with a gestational age of <34, as well as congenital abnormalities or chromosomal anomalies, newborns of mothers suffering from diabetes mellitus, hypertension, pre-eclampsia, and children with metabolic disorders or evidence of congenital infections, as well as those who were born to mothers with clinical chorioamnionitis, were excluded from this study.

Sampling method and sample size

The samples were selected using the census method, and all individuals who met the inclusion criteria were included in the study.

Data collection

Asphyxia neonates were divided into control and case groups. The case group included asphyxia neonates with ARF, and the control group included asphyxia neonates without ARF. Renal failure is defined according to the RIFLE criteria modified for the neonatal period as follows (15).

Table 1. Definition of renal failure according to the RIFLE criteria modified for the neonatal period

	Creatinine criteria	Urine output criteria
	Neonatal RIFLE	Neonatal RIFLE
Risk	Increased Cr×1.5 or GFR decreases >25%	UO <1.5 mL/kg/h for 24 h
Injury	Increased Cr×2 or GFR decreases >50%	UO <1.0 mL/kg/h for 24 h
Failure	Increased Cr×3 or GFR decreases >75% or GFR <35 mL/min/1.73 m^2	UO <0.7 mL/kg/h for 24 h or anuria for 12 h

For all infants with asphyxia, who had renal insufficiency based on serum Cr level or urinary output, the Cr level was checked in the first 8 h after birth, and on the fourth day, urine volume was measured to assess urinary excretion, per kilogram of body weight. The clock was monitored and measured from the first day. Simultaneous with sampling for Cr, blood samples were also sent for checking the level of KIM-1 and cystatin-C. The blood sample was analyzed for each biomarker by special kits through the ELISA method, and the results were thoroughly recorded. The obtained information was entered into SPSS software (version 18) for further analysis. Measurement of serum KIM-1 levels for this assay was conducted using the ELISA method. Wuhan Boster Biological Technology. Ltd. Kits (China) and associated standards were also utilized in this study. The assay range was from 31.2 pg/mL to 2000 pg/mL for KIM-1. Serum Cr concentration was measured by a kinetic colorimetric Jaffe method (Modular P Analyzer, Roche Almere, the Netherlands). For the measurement of the serum cystatin-C levels, the particle enhanced turbidimetric inhibition immunoassay method was employed for this assay. The Abbott ARCHITECT c16000 automatic biochemical analyzer and Biosino Co. Ltd. Kits (China) were also used for measurements.

Statistical analysis

This study used gender-match and age-matching (day) for analysis. Continuous variables were reported as mean±SD, and comparison between the case and control groups was conducted by two independent sample t-tests. As the gender and age-matched pair data were used for analysis, the association between biomarkers with AKI was assessed using conditional logistic regression. Results were reported as odds ratio (OR) with 95% confidence interval (CI) for both crude and adjusted logistic models. In addition, the receiver operating characteristic (ROC) curve analysis was performed to determine the predictive power and critical value of biomarkers as diagnostic factors of AKI in asphyxiated neonates. Statistical analysis was performed in SPSS software (version 18, IBM, Chicago, The United States). A p-value less than 0.05 was considered statistically significant.

Ethical issues

The Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran, approved the ethical considerations of the present study (IR.MUI.MED.REC.1397.043).

Results

This study was conducted on 45 neonates diagnosed with asphyxia, among whom 22 patients had AKI, while 23 cases did not meet the AKI criteria. According to the inclusion and exclusion criteria, one sample from the control group and one sample from the case group were excluded from the study. Comparison of demographic characteristics between the two groups showed no significant differences between cases and controls regarding gestational age, weight, and height at birth (Table 2). Comparison of the Cr within 8 h ($P<0.001$) and 4 days ($P<0.001$) after birth were statistically different between the two groups. Detailed information is presented in Table 2. The mean level of Cr-Standardized KIM-1 8 h and 4 days after birth was significantly higher in the case group, compared to the control group ($P<0.05$) (Table 2). The Cr-Standardized cysteine mean level only 4 days after birth was significantly higher in the case group, compared to the control group ($P<0.05$) (Table 3). Results of the crude and adjusted conditional logistic regression are shown in Table 4. It was observed that 8 h after birth, a one-unit increase in Cr-Standardized KIM-1 level was associated with 54% higher odds of the AKI in the adjusted model (OR: 1.54, 95% CI: 1.03-2.30). A similar finding was observed for Cr-standardized KIM level 4 days after birth (OR: 1.53, 95% CI: 1.01-2.34).

As shown in Figure1 and Table 4, ROC curve analysis demonstrated that between the two biomarkers with two measurements, Cr-Standardized KIM-1 within 4 days had the highest area under the curve (AUC) (0.751, 95% CI: 0.597-0.905). Results of ROC curve analysis showed that Cr-Standardized KIM-1 within 4 days after birth with a critical value of >0.67 ng/ml allowed to predict kidney failure in newborns with 57.1% sensitivity and 86.4% specificity.

Table 2. Demographic characteristics of the participants

Variables	Group	Mean	SD	P-value
Gestational age (week)	Asphyxia with AKI Asphyxia without AKI	38.32 38.00	1.67 1.83	0.55
Weight (gr)	Asphyxia with AKI Asphyxia without AKI	3483.64 3490.91	558.62 475.75	0.96
Height (cm)	Asphyxia with AKI Asphyxia without AKI	47.50 47.68	2.37 2.32	0.80
Cr within 8 hours (mg/dl)	Asphyxia with AKI Asphyxia without AKI	1.0٠ 0.51	0.42 0.12	<0.001*
Cr within 4 days (mg/dl)	Asphyxia with AKI Asphyxia without AKI	1.37 0.50	0.63 0.10	<0.001*

Table 3. Comparison of kidney injury molecule-1 and cysteine Cr-standardized between the case and control groups

8 hours after birth	Group	Mean	SD	P-value
KIM-1 Cr-Standardized (ng/ml)	Asphyxia with AKI Asphyxia without AKI	1.31 0.37	1.67 0.34	0.02*
Cysteine Cr-Standardized (mg/L)	Asphyxia with AKI Asphyxia without AKI	1.83 1.21	1.97 0.80	0.18
4 days after birth Cysteine Cr-Standardized (mg/L)	Asphyxia with AKI Asphyxia without AKI	2.35 0.96	2.77 0.37	0.03*
KIM-1 Cr-Standardized (ng/ml)	Asphyxia with AKI Asphyxia without AKI	1.59 0.48	1.62 0.48	0.006*

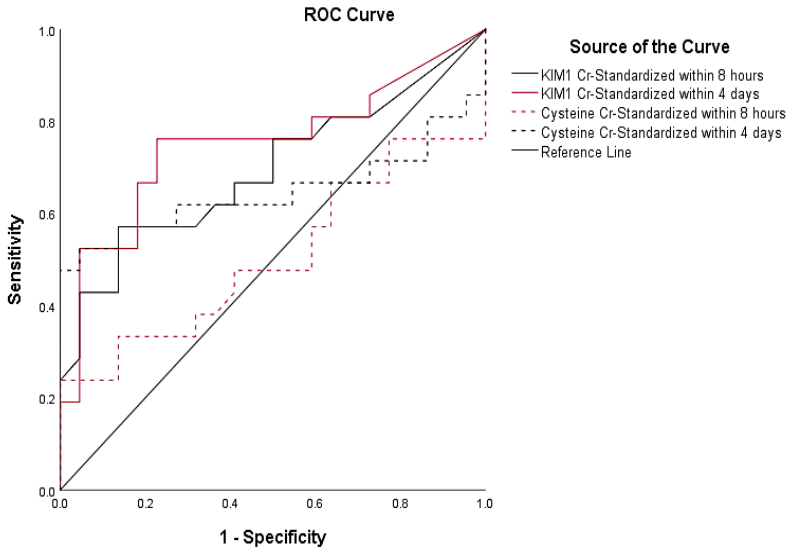

Figure 1. Determination of sensitivity and specificity using rock curve in the present study

Table 4. Association of the kidney injury molecule-1 and cysteine Cr-standardized with acute kidney injury by conditional logistic regression

	Crude			Adjusted		
8 hours after birth	OR	95% CI		OR	95% CI	
KIM-1 Cr-Standardized (ng/ml)	1.33*	1.01	1.76	1.54*	1.03	2.30
Cysteine Cr-Standardized (mg/L)	1.00	0.83	1.20	0.99	0.74	1.32
4 days after birth	OR	95% CI		OR	95% CI	
KIM-1 Cr-Standardized (ng/ml)	1.54*	1.07	2.18	1.53*	1.01	2.34
Cysteine Cr-Standardized (mg/L)	1.18	0.93	1.50	1.11	0.83	1.49

Model adjusted for gestational age, birth weight and height.*A p-value less than 0.05 was considered statistically significant

Discussion

This study aimed to evaluate biomarkers, such as KIM-1 and cystatin-C, which can help detect AKI more rapidly in asphyxiated infants, since they are the most common causes of AKI in infants, regardless of the effect of maternal elements. It is really important to detect AKI as early as possible, just within hours after an insult occurs. If AKI is detected within days following an insult, it may lead to the rise of serum Cr. However, validation of novel AKI biomarkers is impaired by the lack of high quality, sensitive, and specific definition of AKI in neonates (16-18). Since KIM-1 is a diagnostic biomarker, its cut-off point or normal range is not known, though some studies have proposed some estimated figures (15).

In the current case-control study, the efficacy of two markers, KIM-1 and cystatin-C, was assessed among the asphyxiated neonates. Case and controls were similar regarding gestational age, age at study, body weight at birth, and height. This study investigated KIM-1, cystatin-C, and Cr levels in neonates after acute perinatal asphyxia. These markers were checked 8 h and 4 days after birth between those with and without AKI. In the present study, a significant difference in KIM-1 concentration was observed both after 8 h and 4 days of life between asphyxiated neonates with AKI and without AKI. The ROC curve analysis revealed that serum KIM-1 concentration could predict the development of AKI with sensitivity (57.1%) and high specificity (86.1%). Examination of all three biomarkers in the first 8 h of birth shows that Cr and KIM-1 were significantly different between case and control groups, while cystatin-C was not significantly different between the two groups in this time interval. Furthermore, the mean Cr level in the case group was equal to the normal level of Cr for adults, although it cannot be concluded with certainty whether this Cr was due to ARF in the baby or it was derived from maternal Cr. Therefore, it is logical to replace a more appropriate biomarker in such a clinical situation, and based on that, the patient should make a quick decision to avoid mortality and morbidity. Similar studies have been conducted trying to propose suitable markers for the diagnosis of ARF. As a case in point, Vaidya et al. showed that the quantitation of urinary KIM-1 was likely to be very useful for the evaluation of kidney injury in animal pathophysiological studies, as well as predictive toxicology. The results also revealed that it may improve the ability to identify effective therapeutic agents for kidney injury and eliminate nephrotoxic compounds early in the drug development process (19).

In a comprehensive evaluation, Genc et al. assessed the KIM-1 value for AKI detection among preterm neonates (20). They assessed three groups of preterm neonates, including the normal ones, those with respiratory distress syndrome (RDS) but without AKI, and those with simultaneous RDS and AKI. Their eventual findings were consistent with the results of the present study, as they found significantly higher levels of KIM-1 in the AKI group, in comparison with the two others. In another study, Liangos et al. proposed urinary N-acetyl-beta-glucosaminidase and KIM-1 as promising prognostic markers in patients with ARF (21). Khreba et al. confirmed that KIM-1 is an early predictor of AKI in post-cardiopulmonary bypass in open-heart surgery patients (22). Chaturvedi et al. revealed that KIM-1 had great potential as a biomarker of renal injury; moreover, the assay by R&D Co. provided the ability for any researcher to generate KIM-1 data (23) Bonventre et al. showed that KIM-1 was a specific and sensitive biomarker of kidney injury (24).

The findings of the present study indicate that cystatin-C cannot be an early predictor of AKI. No significant differences in serum cystatin-C levels were observed between the groups with and without AKI 8 h after birth. These data are, however, different from those obtained by Li et al. (25) The limitation of using cystatin-C as a factor for the early diagnosis or prediction of AKI in neonates was its increase following sepsis, as well(26). This association between serum levels of cystatin-C and neonatal AKI has been presented by previous studies, as well.

Given the scientific advances and sensitivities that existed in the obstetrics and gynecology department, the researchers were able to collect a small sample size in one year. It seems that such a study on asphyxiated infants worldwide takes more than several years. However, working on case and control groups, all of whom were asphyxiated infants, and the bio-marker-chem check 1 is one of the strengths of this study, which has not been conducted before. Other limitations of this study were the sanctions imposed on Iran and the restricted import of the KIM-1 biomarker diagnostic kit, which forced us to change and reduce the original design of the study, which was checked at various times after birth. It was attempted to do blood sampling with minimal blood and exactly at the time of other diagnostic and therapeutic measures that were ordered for the baby.

Conclusion

The present study showed that high-specificity KIM-1 is a good biomarker for the early detection of ARF in asphyxiated infants; however, similar expectations cannot exist regarding cystatin-C for at least the first 8 h after birth.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

Ethics approval

The Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran, approved the ethical considerations of the present study (IR.MUI.MED.REC.1397.043).

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