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Original article

EARLY DETECTION OF ACUTE KIDNEY INJURY IN PRETERM NEWBORNS WITH PERINATAL ASPHYXIA USING SERUM CYSTATIN

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Abstract: **Introduction:** The diagnosis of acute kidney injury (AKI) in preterm newborns with perinatal asphyxia based on increased serum creatinine (sCr) value and oliguria/anuria is usually delayed. The **Aim** of this paper is to evaluate serum cystatin C as an early predictor of AKI.

Materials and methods:The study included 42 preterm newborns (24-37 weeks) with perinatal asphyxia (Apgar score (AS) ≤ 3 at 5 minutes of life or blood pH on admission ≤ 7.00). The sCr and sCys-C levels were measured on the 1st, 3rd, and 7th day of life. According to KDIGO criteria, the newborns were classified into groups, and sCr and sCys-C values were compared.

Results: The mean gestational age was 29.9 ± 3.0 weeks. AKI was diagnosed in 62.8% of patients. Of these patients, 81.5% belonged to AKI 1 group, and 18.5% to AKI 2 group. No newborns had the criteria for AKI 3. On day 7 the mean sCr values were significantly higher in AKI (65.4 ± 21.8) compared with the non-AKI group (168.4 ± 38.2) ($p < 0.001$), but not on day 1 and 3 ($p = 0.322$, 0.012, respectively). The sCys-C values were significantly higher in the AKI group on day 3 (AKI vs. non-AKI group, 0.69 ± 0.22 vs. 1.22 ± 0.20; $p < 0.001$) and day 7 (AKI vs. non-AKI group, 0.62 ± 0.41 vs. 1.68 ± 0.20; $p < 0.001$). The sCys-C was also an earlier marker of a more severe stage of AKI than sCr.

Conclusion: The sCys-C was elevated earlier than sCr, making it a valuable diagnostic tool for AKI in preterm newborns.

Keywords: preterm newborn, perinatal asphyxia, acute kidney injury, biomarkers, cystatin C.

INTRODUCTION

The improvement in the treatment of preterm newborns significantly raised their survival rate, but the residual morbidity and mortality are still very high. Various pathological conditions caused by perinatal asphyxia are called Oxygen Radical Diseases of Prematurity (ORDP) (1). One of the most common conditions in this category is acute kidney injury (AKI) of the newborn. There are various clinical criteria for the diagnosis and classifying of AKI, including the RIFLE (2), AKI Network (AKIN) (3), and Kidney Disease Improving Global Outcomes (KDIGO) (4). RIFLE classifies AKI based on the elevation of sCr value in relation to the basal value and reduction of diuresis in 3 stages (Risk, Injury, Filure) and two clinical outcomes (Loss of kidney function, End-stage renal disease) (2). Some studies indicated deficiencies in RIFLE criteria. They showed that even a slight increase (0.3-0.5 mg/dl) sCr increased mortality three times, while an increase higher than 0.5 mg/dl increased mortality up to eighteen times (3). Therefore, the working group of nephrologists and intensivists under the name Acute Kidney Injury Network (AKIN) proposed its definition of AKI (3). Significant changes made by the AKIN system concerning the RIFLE criteria are: a) the interval for the first assessment of any AKI stage is 48 hours (7 days in the RIFLE system); b) stage 1 is extended to sCr value 0.3 mg/dl, and c) patients treated with any methods of renal replacement therapy are classified in stage 3 regardless of sCr values or diuresis (3). The introduction of another classification system complicated the diagnosis, grading, prevention, and treatment

Table 1. *Neonatal AKI staging – KDIGO 2012 (4)*

Stage	SCr (mg/dl)	Urine output (ml/kg/h)
0	No change in SCr or rise < 0.3 mg/dl	≥ 0.5 mL/kg/h
1	S Cr rise ≥ 0.3 mg/dl within 48 h or SCr rise ≥ 1.5-1.9×reference SCr	< 0.5 mL/kg/h for 6-12
2	SCr rise ≥ 2.0-2.9×reference SCr	< 0.5 mL/kg/h for ≥ 12h
3	SCr rise ≥ 3×reference SCr orSCr ≥ 2.5 mg/dl	< 0.3 mL/kg/h for ≥ 24h or anuria for ≥ 12h

Scr- serum creatinine

of AKI, especially in the pediatric population. To find a compromise and reconcile the differences between AKIN and RIFLE criteria, a global organization developing and implementing evidence-based clinical practice guidelines in kidney diseases – KDIGO, introduced a unique definition and grading of AKI (Table 1). Still, all these classification systems are based on the values of serum creatinine and/or urine output. In the first days of life, the usefulness of these parameters is limited by the influence of maternal sCr level, developing renal physiology, and unreliable assessment of diuresis. On the other hand, sCr and diuresis do not provide any information about the site of kidney disease. There is also a practice of following diuresis without other parameters of renal function, which can be dangerously misleading in identifying patients with a neo-oliguric type of AKI (5). This makes sCr and diuresis insufficient in the diagnosis of AKI in newborns. There is a constant search for biological markers that can be used in diagnosing AKI, especially in its early phase. Among the first biomarkers discovered in urine was cystatin-C, a cysteine protease inhibitor that is synthesized and released into the blood at an almost constant rate by all nucleated cells. It is freely filtered in the glomeruli, completely reabsorbed in the proximal, and not secreted in the distal tubule, which makes it a promising endogenous biomarker of glomerular filtration (GF) (6).

In this study, we wanted to estimate if serum cystatin C (sCys-C) can be used as a diagnostic tool for AKI in preterm newborns.

MATERIAL AND METHODS

This was a prospective study of premature asphyxiated newborns 24-32 weeks of gestation admitted to the Neonatal Intensive Care Unit University Medical Center Sarajevo between October 2020 and October 2022. This study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013) and the General Data Protection Regulation (GDPR). Informed parenteral consent was given for all participating newborns.

The indicator of perinatal asphyxia was AS ≤ 3 in the fifth minute of life or blood pH on admission ≤ 7.00. The premature newborns included in the study also met the following criteria: (1) absence of congenital anomaly of the kidneys and urinary tract; (2) absence of a congenital anomaly of the heart or large blood vessels; (3) absence of any genetic disease, metabolic disease or any other anomaly. AKI was diagnosed based on an increase in the value of serum creatinine compared to the basal value and urine output (Table 1.). The lowest previous value of sCr served as its basal value.

The sCr and sCys-C levels were measured on the 1st, 3rd, and 7th day of life (the date of birth was equal to postnatal day 1). SCr was determined using the Jaffe kinetic spectrophotometric method. The sCys-C level was measured with the ELISA assay and the reference interval was calculated nonparametrically to be 0.53-0.95 mg/L. Diuresis was measured in all included preterm newborns. They did not receive diuretics in the first 48 hours of life.

According to KDIGO criteria, the newborns were classified into two groups AKI or non-AKI group. That was the primary division, and then the AKI group, according to the standards of the KDIGO classification, was divided into subgroups (AKI 1 or AKI 2). In our study, there were no registered AKI 3 cases.

The laboratory tests were blinded to the clinical outcomes.

Statistical analysis was performed using IBM SPSS statistics version 20.0 and P values less than 0.001 were considered significant. The groups were compared using the Student *t*-test and Mann–Whitney test. Multivariate logistic regression was used to assess the development of AKI.

RESULTS

All newborns were divided into two groups: the AKI group, a larger group of newborns who developed AKI 27 (64.3%), and the non-AKI group, a smaller group of 15 (35.7%) newborns without AKI. There were no significant differences between AKI and non-AKI, as well as AKI 1 and AKI 2 groups regarding sex and gestation age (GA). Values of pH in the AKI and AKI 2 groups were lower than in the non-AKI and

Table 2. *The basic clinical features and values of sCr and sCys-C of included premature newborns*

	Total (n = 42) n (%)	Non- AKI (n = 15) n (%)	AKI (n = 27) n (%)	p	AKI 1 (n = 22) n (%)	AKI 2 (n = 5) n (%)	p
Sex (male)	23 (54.8)	13 (56.52)	10 (43.48)	0.144	14 (51.85)	13(48.1 5)	0.132
GA, wk (mean, ± SD)	28.8 ± 4.0	29.4 ± 2.4	28.5 ± 3.0	0.181	28.1 ± 3.2	29.1 ± 3.5	0.024
Inotropes	30 (71.43)	6 (40)	24 (88.89)	< 0.001	20 (90,91)	4 (80)	0.014
Blood pH on admission	6.95 ± 0.4	7.0 ± 0.5	6.84 ± 0.3	0.102	6.92 ± 0.3	6.97 ± 0.2	0.123
sCr Day 1	108.4 ± 21.2	88.7 ± 16.2	115.4 ± 28.2	0.322	98.4 ± 21.2	105.7 ± 26.2	0.422
sCr Day 3	138.4 ± 41.2	80.4 ± 30.2	128.4 ± 38.2	0.012	140.4 ± 31.2	178.4 ± 41.2	0.002
sCr Day 7	150.4 ± 36.8	65.4 ± 21.8	168.4 ± 38.2	< 0.001	154.0 ± 33.9	218.4 ± 36.3	< 0.001
sCys-C Day 1	0.79 ± 0.85	0.73 ± 0.35	0.81 ± 0.20	0.355	0.80 ± 0.43	0.83 ± 0.13	0.145
sCys-C Day 3	0.85 ± 0.25	0.69 ± 0.22	1,22 ± 0.20	< 0.001	1,01 ± 0.26	1.38 ± 0.48	0.001
sCys-C Day 7	0.88 ± 0.	0.62 ± 0.41	1.68 ± 0.20	< 0.001	1.81 ± 0.55	1.61 ± 0.32	0.001

GA, gestational age; nCPAP, sCr, serum creatinine, sCys-C, serum cystatin C
P < 0.001 is considered statistically significant

AKI 1 groups, respectively, but the difference was not statistically significant.

AKI was associated with significantly higher mortality. 5 of 27 newborns (18.51%) with AKI died versus 1 of 15 (6.67%) without AKI (odds ratio (OR) 6.97, 95% confidence interval (CI), 4.3–15.0; P < 0.001]. Only one newborn of the AKI 2 group survived.

On days 1 and 3, the mean sCr values were not significantly higher in AKI compared to non AKI group (p = 0.322, 0.012, respectively). The mean sCr values became significantly higher in the AKI group on day 7 (P <0.001). When comparing AKI 1 and AKI 2 groups, the difference in mean sCr values was statistically significant only on day 7.

The mean sCys - C in the AKI group was not significantly higher compared to non AKI group only on day 1 (p = 0.355). On days 3 and 7, the mean sCys-C values were significantly higher in AKI compared to non AKI group (P <0.001). The difference in sCys-C values between AKI 1 and AKI 2 was not significant only on day 1 (p = 0.145). On days 3 and 7, the mean sCys-C values were significantly higher in AKI 2 compared to AKI 1 group (P <0.001) (Table 2.).

DISCUSSION

AKI in preterm newborns is a severe clinical syndrome with a high mortality rate (7). Both, serum creatinine and diuresis are late consequences of kidney injury and not a marker of the injury itself. The physiological characteristics of the preterm newborn make the interpretation of these parameters challenging (8,9). The general belief is that newborns have non-oliguric AKI (10), but this may be misleading in the absence of knowledge about the normal diuresis of the newborn, which changes with tubule maturation (10).

Neonatal AKI has long been considered a reversible syndrome. But recently, the long-term prognosis of AKI has been studied more seriously. In one study, out of 126 neonates who were followed up to three years after an episode of AKI, 10% developed a chronic kidney disease (CKD), which was directly correlated with AKI (11). One study evaluated the long-term AKI consequences in the newborn population (12), but generally, the evaluation studies of CKD after an AKI episode are missing. The early diagnosis of AKI in preterm newborns is crucial for early initiation of therapy, starting diuretic therapy in oliguric patients, and adjusting medication doses and fluid intake to sustain or achieve the homeostatic balance. That way, we could minimize the long-term consequences of AKI (13,14). With that goal, the difficulties with timely diagnosis of AKI are trying to be solved with new biomarkers of AKI. They are expected to have a prominent importance in newborns. Recent research efforts have led to the development of prospective studies of biomarkers for the early detection of AKI, but the number of studies on newborns is still limited (15,16,17). Our study showed that the diagnosis of AKI based on conventional biomarkers is delayed by 48-72 hours compared with sCys.C. Our ability to diagnose AKI early may improve more by combining several biomarkers, which would improve therapeutic and preventive measures and AKI prognosis.

CONCLUSION

The sCysC level was found to have a statistically significant association with the development of AKI in

preterm neonates with perinatal asphyxia, and it elevated earlier than sCr. This makes it a good predictive marker for AKI in preterm newborns. New biomarkers of neonatal AKI need to be introduced into the standard diagnostic protocol in pediatric intensive care units and neonatology wards.

Abbreviations

AKI — acute kidney injury
AKIN — Acute Kidney Injury Network
GA — gestational age
KDIGO — Kidney Disease Improving Global Outcomes
nCPAP — nasal continuous airway pressure
RIFLE — Risk Injury and Failure Classification
sCr — serum creatinine
sCys-C — serum cystatin C

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Sažetak

RANO OTKRIVANJE AKUTNOG OŠTEĆENJA BUBREGA KOD NEDONOŠČADI S PERINATALNOM ASFIKSIJOM PRIMENOM SERUMSKOG CISTATINA

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Uvod: Dijagnoza akutnog oštećenja bubrega (AOB) kod nedonoščadi s perinatalnom asfiksijom na osnovu povećane vrednosti serumskog kreatinina (sCr) i oligurije/anurije obično se kasni. **Cilj** ovog rada je procena vrednosti serumskog cistatina C kao ranog prediktora AOB.

Materijali i metode: Studija je obuhvatila 42 nedonoščadi (24-37 sedmica) sa perinatalnom asfiksijom (Apgar skor (AS) ≤ 3 na 5 minuta života ili pH krvi pri prijemu ≤ 7,00). Nivoi sCr i sCys-C mereni su 1, 3 i 7 dana života. Prema KDIGO kriterijumima novorođenčad su klasifikovana u grupe i upoređene su vrednosti sCr i sCys-C.

Rezultati: Prosečna gestacijska dob bila je 29,9 ± 3,0 sedmice. AOB je dijagnostikovan kod 62,8 % pacijenata. Od ovih pacijenata, 81,5% je pripadalo grupi AOB 1, a 18,5% grupi AOB 2. Nijedno novorođenče nije imalo kriterijume za AOB 3. Sedmog dana srednje vrednosti sCr bile su značajno veće kod AOB (65,4 ± 21,8) u poređenju sa ne-AOB grupom (168,4 ± 38,2) ($p < 0,001$), ali ne 1. i 3. dan ($p = 0.322$, 0.012, respektivno). Vrednosti sCys-C bile su značajno veće u AOB grupi 3. dana (AOB naspram ne-AKI grupe, 0,69 ± 0,22 naspram 1,22 ± 0,20; $p < 0,001$) i 7. dana (AOB naspram grupe bez AOB, 0,62 ± 0,41 vs. 1,68 ± 0,20; $p < 0,001$). SCys-C je takođe bio raniji marker ozbiljnijeg stadijuma AOB od sCr.

Zaključak: SCys-C je povišen ranije od sCr, što ga čini vrednim dijagnostičkim sredstvom za dijagnostikovanje AOB kod nedonoščadi.

Ključne reči: nedonošče, perinatalna asfiksija, akutno oštećenje bubrega, biomarkeri, cistatin C.

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