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Importance of Determination of Urine Neutrophile Gelatinase Associated Lipocalin in Early Detection of Acute Kidney Injury

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A B S T R A C T

Acute kidney injury (AKI) is a complex, frequent and serious clinical problem with high rate of mortality. Therefore there is a serious need for early detection of AKI, with a tendency to detect early stage – RISK dut to start with therapy as soon as possible and prevent irreversible changes in renal function. Study's purposes were to explore the rhythm of urine neutrophile gelatinase associated lipocalin (urine NGAL) concentration changes before and after cardiovascular surgery and compare results of urine NGAL values with results of serum creatinine and creatinine clearance as main diagnostic indicators of renal function in order to define role of urine NGAL biomarker in early diagnosis of acute kidney injure. In the prospective clinical study 150 cardiovascular surgery patients were included. Basal value and concentration of urine NGAL were tested 3, 6 and 12 hours after cardiovascular surgery, and concentration of serum creatinine was tested once per day first three days after surgery. Also creatinine clearance value was calculated according to Cockrof-Goult formula. After above mentioned, rate of acute kidney injure was estimated according to RIFLE criteria. The study results showed that the value of urine NGAL was elevated above cutt-off after cardiac operation in a group of patients who developed AKI (defined according to RIFLE criteria). There were statisticaly significant difference between all four measerments ($p<0.05$). There were also moderate positive correlation (0.500 and 0.502) between urine NGAL values and percentage difference of serum creatinine and creatinine clearence. All that indicate that higer values of urine NGAL are followed by higher percentage difference of serume creatinine and creatinine clearence. By using of automated urine NGAL test detection of acute kidney injure is posible 24–48 hours earlier comparing with actual results acquired by determination of serum creatinine concentration. The results of this study will indicate urine NGAL as a reliable biomarker of early acute kidney injure. A combination of early and late markers of kidney damage (urine NGAL, serum creatinine) can greatly contribute to better control the outcome of all those who are a risk group for the development of AKI.

Key words: *urine neutrophile gelatinase associated lipocalin, acute kidney injure, RIFLE criteria*

Introduction

Acute kidney injury occurs as a complication in approximatelly 2–5% hospitalised patients, whereas up to 30% of admitted patients in intensive care units (ICU) develops this complication[1]. Mortality associated with AKI is appoximatelly 50%. Percentage of survival is considerably lower in patients who developed acute kidney injury compared to the patients who have not experienced such type of injury. Approximatelly 50% of patients who survive an acute kidney injury, develope subclinical impairment of kidney function. The kidney function is never recovered in approximatelly 5% of patients and it requires prolonged dialysis or transplantation treatment[2]. Early diagnostics of initial kidney injury and prevention of further effects of detrimental factors is of immense importance. In addition to specific clinical indicators, urin analysis and determination of kidney failure index, very important AKI indicator can be obtained through laboratory findings. In this regard, the serial serum creatinine measurements have been used as the main AKI diagnostic indicator for the last 50 years[3]. The practice to date indicates that the use of serum creatinine in detecting of early kidney failure has been limited

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because it dependens on a number of extra-renal factors. Therefore, there is a justified need to develop and apply new biomarkers which will contribute to quality and reliable diagnostics of acute kidney injury, in order to achieve timely therapeutic effects. Such biomarker should be specific and easily measurable. It should also provide reproducible results, correlate with severity of condition, indicate the severity of renal injury even when no typical clinical signs are present, and indicate, in timely manner, the need to introduce therapy[4]. Measurement of urinary NGAL levels, as a marker for ishemic and nephrotoxic injury to renal parenchyma, anticipates the possibility to identify, more precisely, the occurrence and early diagnosis of acute kidney injury which is particularly important in monitoring and treatment following the cardiovascular surgeries, where AKI development is mostly combined with ischemic impairment of renal perfusion or reduction of renal reserve[5–7]. The studies show that increase of NGAL concentrations occurrs 24–48 hours earlier in comparison with the increase of serum creatinine after the cardiac surgery[8].

The objective of this study was to investigate dynamics of urine NGAL changes in patients before and after cardiovascular surgeries, to compare the obtained urine NGAL values with serum creatinine and creatinine clearance values, being the main diagnostic indicators of renal function, and to determine whether the urine NGAL has a role of a biomarker in an early detection of acute renal injury.

Patients and Methods

Patients

Prospective clinical trial was conducted in May 2010–July 2012 period, in the Clinical Center of Sarajevo University, in an intensive care unit (ICU) of the Cardiac Surgery Clinic. The trial included 150 patients above the age of 18 (both genders), who underwent cardiovascular surgery, were admitted to intensive care unit and hospitalised for more than 24 hours. The patients with the existing chronic renal insufficiency, the chronic hemodialysis patients, patients receiving peritoneal dialysis, patients with existing peripheral vascular diseases, patients suffering from diabetes mellitus, patients who used nephrotoxic drugs prior to the study (aminoglycosides, non-steroidal anti-inflammatory drugs, etc.), patients under the 18 years of age, hospitalised for less than 24 hours, patients with confirmed infection of upper urinary tract or hematuria, were not included in the study. Medical records of patients were used (history), which gave an insight to laboratory, clinical and demographic data. Urine samples were collected from each patient to determine NGAL concentration in urine whereas blood samples were taken to determine serum creatinine and urea levels. Creatinine clearance was calculated using the Cockcroft-Gault formula (equation). The laboratory findings of patients with confirmed normal preoperative kidney status were used to assess development of AKI in postoperative period. The former researches show that monitoring of daily diuresis in patients, following the cardiac surgery, is not relevant in assessing the development of acute kidney injury due to excessive use of diuretics in treatment of these patients. Thus, the use of this parameter in the mentioned group of patients is not considered relevant. Due to the same reason, the mentioned parameter was not taken into consideration.

Methods

Upon admission, basal renal function was determined for each patient, based on the data on serum creatinine concentration and calculated creatinine clearance, which were obtained prior to the surgery. During the hospitalisation, all patients were evaluated through collection and analysis of the monitored parameters. Urine NGAL concentration was measured 3, 6, and 12 hours after the completion of surgical procedure, whereas serum creatinine was measured once a day during the first three days following the surgery. Measurement of NGAL and creatinine concentrations was conducted using the automated immuno-biochemical analyser, the so called Architect ci8200, of company Abbott Laboratories. In order to measure urine NGAL concentration, the Chemiluminescent Microparticle Immunoassay Technique (CMIA) was applied. The reagents, used in biochemical reaction, contain designed antibodies which may bind to epitopes on NGAL molecule. Architect NGAL test had a functional sensitivity <2 ng/mL and total coefficient of variation (CV) less than 5%. NGAL cutt-of value is 100 ng/mL[9]. According to Bennet's modified RIFLE Classification for AKI, conducted against the value of NGAL in urine[8], NGAL values <100 ng/mL are considered normal, values ranging from 101–200 ng/mL are considered an early stage of AKI (Risk – R), values ranging from 201–300 ng/mL correspond to AKI Injury stage (I), whereas the values >300 ng/mLl correspond to AKI Failure stage (F). The urine sample intended for measurement of NGAL concentration was sent to laboratory for analysis, immediately after having been collected. When it was necessary to postpone the testing, the sample was stored in refrigerator at 2–8 °C for the period of 7 days, of for the longer period at –70 °C. Serum creatinine concentration was measured by modified kinetic Jaffeove reaction (method) on Laser Nephelometer BN II. Serum urea concentration was measured by the standard ureasis laboratory method (modified Talke and Schubert enzymatic procedure) on Architect ci8200. Determination of kidney function following the surgery was conducted based on the monitoring of daily changes of serum creatinine. Creatinine clearance ($eC_{Cr)}$ was assessed using the Cockcroft-Gault formula[10]. The normal renal function is determined by the value of creatinine clearance ≥90 mL/min. Creatinine clearance was calculated using the Cockcroft-Gault formula:

$$eC_{Cr=} \frac{(140 - \text{years}) \text{ x body weight (kg)} \text{ (x 0,85 for women)}}{72 \text{ x serum creatinin } (\mu\text{mol/L})}$$

Diagnosis and assessment of the severity of acute kidney injury was conducted in line with RIFLE criteria[11,12], where an increase in serum creatinine ≥26.2 μmol/L from baseline within 24 hours or 1.5-fold increase of serume

creatinine from baseline, or decrease of creatinine clearance by 25% from baseline for minimum 3 days, i.e. diuresis less than od 0.5 mL/kg/hour for the period exceeding 6 hours[13], is considered an early stage of acute kidney injury, according to this classification. Application of RIFLE criteria enables the patients to be stratified with regard to various levels of their kidney injury based on severity (risk, injury, failure) and an outcome (loss, end stage).

Statistics

The statistical methods used for data processing were as follows: average value ($\overline{X}$ – arithmetic mean), standard deviation (SD), median (mean value), minimum value, maximum value, and 25^{th}–75^{th} percentiles. Distribution values of analysed variables were assessed using the D'Agostino-Pearson test. The dependent samples Student's t test was used to assess the differences within the groups. Friedman test (F) »double analysis of variance by ranks« was conducted to assess the differences between the results obtained within the group. One-way analysis of variance was applied in the analyses of results obtained through repeated measurements which satisfied the normal distribution conditions. The correlation range was assessed using Spearman's rank correlation coefficient. Accepted statistical significance was $p<0.05$. Statististical analyses were conducted in Med Calc statistical software for Windows, version 12.2.1.0. (MedCalc Software, Mariakerke, Belgium).

Results

The study included 150 patients, with the average age of 59.46±10.14, average body weight 84.36 kg±14.74 and average height 172.53 cm±8.18. Out of total number of respondents, 108 were males, while 42 respondents were females. Based on preoperative serum creatinine concentrations, as well as the values obtained after the first, second and third day after surgery, and in line with RIFLE classification of acute kidney injury, the patients were stratified in the group of respondents with no AKI (normal findings), risk group (R), injury group (I) and failure group (F) (Table 1). The largest number of patients with normal findings was identified on the first day after the surgery (144), whereas the largest number of patients who developed an injury was identified on the third day of postoperative measurement (14). Median value of urine NGAL indicates elevation of postoperative urine NGAL in all three measurements, i.e. 3, 6 and 12 hours after the surgery (5.50 ng/mL vs. 6.45 ng/mL *vs.* 9.80 ng/mL), compared to preoperative values (3.65 ng/ml) in patients who developed AKI, defined in line with the RIFLE criteria (Table 2). The results of Friedman test (F) demonstrate a significant difference in urine NGAL concentrations in four different periods (before the surgery, and than three, six and twelve hours after the surgery), ($F(3, 450, N=600)=72.0655$, $p<0.001$) in all patients who developed AKI. Correlation analysis was conducted to assess NGAL values in all measurements (three, six and twelve hours after the surgery) and percentage differences in serum creatinine values. The moderately positive correlations of significant importance were obtained, which indicate that higher NGAL values correspond to more considerable percentage differences in serum creatinine. The most considerable correlation was confirmed between urine NGAL values obtained 12 hours after the surgery and percentage difference between serum creatinine values obtained in the first and the fourth measurement (Table 3). According to urine NGAL cut-off value of 100 ng/mL, it was established that urine NGAL values were elevated in 21 respondents, out of which the majority had values ranging from 101 to 200 ng/ml in all three measurements. The largest number of respondents with elevated urine NGAL values was reported 12 hours after the surgery (Table 4, Figure 1). With regard to the above mentioned, it is evident that, using the test to determine urine NGAL, it is possible to identify acute kidney injury

TABLE 1
DISTRIBUTION OF PATIENTS ACCORDING TO RIFLE CRITERIA OF AKI

Time	Number of patients		
	First day	Second day	Third day
Without of AKI	144	137	130
Risk (R)	5	8	6
Injury (I)	1	4	12
Failure (F)	0	1	2
Total	150	150	150

TABLE 2
NGAL VALUES IN THE URINE BEFORE AND AFTER SURGERY

	NGAL1 (ng/mL)	NGAL2 (ng/mL)	NGAL3 (ng/mL)	NGAL4 (ng/mL)
N	150	150	150	150
$\overline{X}$±SD	7.09±9.49	30.50±91.38	27.40±61.20	37.77±91.98
Median	3.65	5.50*	6.45†	9.80§
95% CI for Median	2.50–5.00	3.80–7.14	5.25–8.19	7.01–11.29
IQR	8.50	3.90	4.40	17.82

NGAL1 – Urine NGAL preoperative value; NGAL2 – Urine NGAL value three hours after surgery; NGAL3 – Urine NGAL value six hours after surgery, NGAL4 – Urine NGAL value twelve hours after surgery, IQR – Interquartile range; *$p<0.05$ difference between NGAL2 and NGAL1; †$p<0.05$ difference between NGAL3 and NGAL1; §$p<0.05$ difference between NGAL4 and NGAL1

TABLE 3
CORRELATION BETWEEN VALUE OF URINE NGAL AND THE PERCENTAGE DIFFERENCES OF SERUM CREATININE IN THE DEFINED MEASUREMENT PERIODS

	NGAL2 (ng/mL)	NGAL3 (ng/mL)	NGAL4 (ng/mL)
	r	r	r
Percentage difference of creatinine 1	0.399*	0.353*	0.286**
Percentage difference of creatinine 2	0.438*	0.428*	0.469*
Percentage difference of creatinine 3	0.468*	0.478*	0.500*

NGAL1 – urine NGAL preoperative value, NGAL2 – urine NGAL value three hours after surgery, NGAL3 – urine NGAL value six hours after surgery, NGAL4 – urine NGAL value twelve hours after surgery; Percentage difference of creatinine 1 – between value of serum creatinine preoperative and first postoperative day; Percentage difference of creatinine 2 – between value of serum creatinine preoperative and second postoperative day; Percentage difference of creatinine 3 – between value of serum creatinine preoperative and third postoperative day
r=coefficient of correlation; *p<0.0001; **p=0.0004

TABLE 4
PATIENT CLASSIFICATION ACCORDING TO THE VALUE OF URINE NGAL IN THE DEFINED MEASUREMENT PERIODS

NGAL ng/ml	Preoperative value (N)	3 hours after surgery (N)	6 hours after surgery (N)	12 hours after surgery (N)
<100	150	139	134	130
101–200	0	6	14	16
201–300	0	1	1	1
>300	0	4	1	3
Total	150	150	150	150

N – number of patients; normal findings of urine NGAL 0–100 ng/mL, risk stage: urine NGAL 101–200 ng/mL, injury stage: urine NGAL 201–300 ng/mL; failure stage: urine NGAL over 301 ng/mL

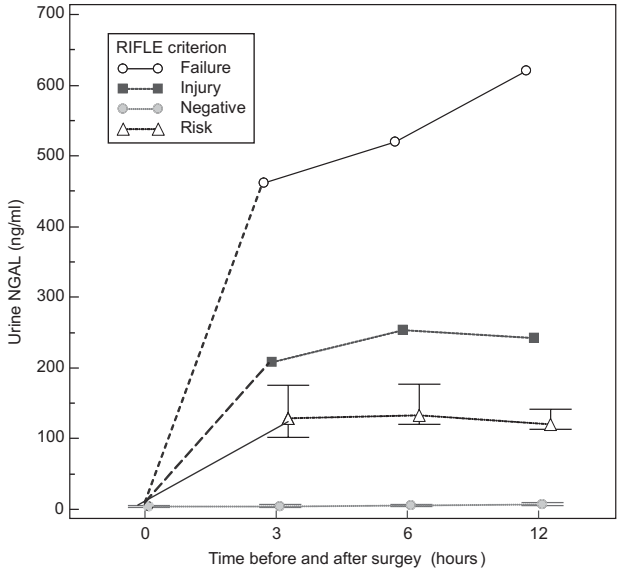

Fig. 1. Patient distribution according to RIFLE criterion in relation to the value of urine NGAL.

24–48 hours earlier compared to dynamics of changes of serume creatinine concentrations. If we use the results obtained by measuring serum creatinine, the largest number of positive results is obtained only 48 hours later, and these results, according to RIFLE classification, fall under the Injury group (I).

Discussion

The acute kidney injury constitutes a complex, frequent and serious problem. It should be emphasised that the AKI-related mortality remains 50% and it has not seen significant changes over the course of the past 30 years. The percentages are particularly high in intensive care units, ranging from 46% to 88%. Thus far, the detection and differential diagnosis have been based on a single marker – serum creatinine. Unfortunately, serum creatinine concentration reveals no changes until a significant injury or loss of nephron function occurs. Chertow et al demonstrated that serum creatinine elevation of ≥0.3 mg/dL in hospitalized adults is directly associated with the fourfold increase in the risk of morbidity, even in patients with controlled diabetes, heart condition and factors such as age of the patient[15]. The RIFLE and AKIN criteria have been extensively validated in more then 550 000 patients, it was demonstrated that serum creatinine elevation of 50% is directly associated with increase of mortality in patients[16]. It is for these reasons that various recently conducted studies analysed new biomarkers. The studies investigate and seek to identify a biomarker which would be characterized by increased production and exertion in damaged cells, while the production and exertion would be negligible in healthy cells. Elevated concentration of such biomarker should occur during the early phase in which the injury remains reversible and it should be proportional with the severity of

the injury; while the reduction in concentration should correlate with the absence of kidney injury. The dynamic changes in concentration should also enable monitoring of the therapeutic effect. The biomarker should be such that it is simple to determine by a non-invasive method. In addition, it should be easily measurable, associated with the pathophysiology of the condition and prognostically relevant. Our study followed the changes in urine NGAL concentration in patients who underwent cardiac surgery. The advantage to determining NGAL in urine is that the samples are collected non-invasively and the likelihood of interference with other protein molecules is reduced, while the diagnostic method itself is performed quickly. During cardiac surgery the most frequent mechanism of AKI is renal vasoconstriction and microvascular injury, leading to prolonged renal ischemia, renal hypoperfusion and ischemic reperfusion injury[17]. The reason for selecting this particular group of patients is that it is possible to determine the biomarker immediately after the surgery and to monitor possible development of AKI. Availability of adequate and well substantiated supporting documentation constitutes an additional reason in this regard. Our study verified acute kidney injury (AKI) in 14% of patients monitored after cardiovascular surgeries. We have confirmed that NGAL is simple to measure and that the excretion of NGAL is heightened in case of injury, while the excretion seen in healthy cells is negligible (control group). Elevation of urine NGAL concentration was measured already three hours after surgery, while the most significant correlation between urine NGAL value and prercentage difference of serum creatinine was measured 12 hours after surgery. Results of this study demonstrate that elevation of urine NGAL concentration occurs 24–48 hours earlier as compared to serum creatinine, the previously used biomarker, which is in line with the studies conducted for the same purposes[8,18,19]. The results suggest that it is possible to identify early stage of acute kidney injury based on single time point measurements of NGAL conducted in the period between 3 and 12 hours, as opposed to serial measurements of serum creatinine, that do not allow for monitoring of sudden changes in renal function. According to the results obtained, it is possible to conclude that urine NGAL is the marker for early detection of AKI, while serum creatinine is the marker for late detection which allows for monitoring of further course of development, recovery or impairment of renal function. The study reconfirmed the usefulness of application of RIFLE classification. In addition, it reconfirmed that by combining the biomarkers it is possible to achieve significant improvements as regards diagnosis, monitoring and therapy of AKI. The respondents monitored according to the risk group criteria exhibited significantly increased risk to develop injury and experience impaired renal function. A clear difference between all four measurements of urine NGAL was recorded. The difference between the baseline values and the values measured after a surgery in patients who developed AKI was particularly significant. The recorded difference ranged from being 10 to 100 times higher, whereby the urine NGAL clearly indicates the early nephron impairment at the stage when the changes are reversible and it is possible to intervene in due time and achieve effects in terms of reducing the morbidity and mortality rates. Majority of studies conducted thus far demonstrated that NGAL is closely associated with AKI in patients with normal renal function prior to surgery and glomerular filtration value of $\geq$60 ml/min[20]. Further research is needed, particularly in the group of patients with coexisting pathology, such as chronic kidney disease, cardiac decompensation and cardiorenal syndrome, systemic infections, systemic inflammatory conditions and malignancy. In conclusion, results of the study indicate significant positive correlation between urine NGAL concentration and serum creatinine values, i.e. creatinine clearance. The highest correlation was recorded 12 hours after surgery. Therefore, we may conclude that the factor of time plays an essential role in detection of acute kidney injury. Undoubtedly, there is a need for early detection of AKI, aiming at detection of the earliest RISK stage, which allows for timely intervention and prevention of irreversible changes in renal function, as well as differential diagnosis of AKI.

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ZNAČAJ ODREĐIVANJA URINARNOG LIPOKALINA UDRUŽENOG SA NEUTROFILNOM GELATINAZOM U RANOJ DETEKCIJI AKUTNOG BUBREŽNOG OŠTEĆENJA

S A Ž E T A K

Akutno bubrežno oštećenje (ABO, eng. AKI) je kompleksan, čest i ozbiljan klinički problem, sa visokom stopom mortaliteta. Zbog toga postoji ozbiljna potreba za detekcijom ABO, s namjerom da se otkrije u ranoj, RISK fazi – kako bi se sa terapijom počelo što je prije moguće te kako bi se spriječile nepovratne promjene bubrežne funkcije. Svrha studije bila je da se ispita dinamika promjena koncentracija lipokalina udruženog sa neutrofilnom gelatinazom u urinu (urinski NGAL) prije i nakon kardiovaskularne operacije te da se rezultati urinarnog NGAL-a usporede sa rezultatima serumskog kreatinina i klirensa kreatinina kao glavnih dijagnostičkih indikatora bubrežne funkcije kako bi se utvrdila uloga biomarkera u vidu urinarnog NGAL-a u ranoj dijagnozi akutnog bubrežnog oštećenja. Prospektivnom kliničkom studijom bilo je obuhvaćeno 150 pacijenata podvrgnutih kardiovaskularnim operativnim zahvatima. Osnovna (početna) vrijednosti i koncentracija urinarnog NGAL –a testirane su 3, 6 i 12 sati nakon kardiovaskularne operacije, a koncentracija kreatinina u serumu testirana je jednom dnevno, tijekom prva tri dana nakon operacije. Također, vrijednost klirensa kreatinina računata je prema Cockrof-Goult formuli. Nakon gore navedenog, stopa akutnog bubrežnog oštećenja procijenjena je u skladu sa RIFLE kriterijima. Rezultati studije su pokazali da se vrijednost urinarnog NGAL-a povećala iznad granične tj. pražne (eng. cut-off) vrijednosti nakon kardiokirurške intervencijie u grupi pacijenata kod kojih se javilo AKI (definirano prema RIFLE kriterijima). Između sva četiri mjerenja postojala je statistički značajna razlika ($p<0.05$). Postojala je i umjereno pozitivna korelacija (0,500 i 0,502) između vrijednosti urinarnog NGAL-a i procentualne razlike kreatinina u serumu i klirensa kreatinina. Sve ovo ukazuje da su više vrijednosti urinarnog NGAL-a praćene većim procentualnim razlikama serumskog kreatinina i klirensa kreatinina. Korištenjem automatiziranog testa za urinarni NGAL, akutno bubrežno oštećenje moguće je detektirati 24–48 sati ranije u poređenju sa stvarnim rezultatima dobivenim određivanjem koncentracije serumskog kreatinina. Rezultati ove studije će pokazati da je urinarni NGAL pouzdan biomarker za rano akutno bubrežno oštećenje. Kombinacija ranih i kasnih markera bubrežnog oštećenja (urinarni NGAL, serumski kreatinina) može u velikoj mjeri doprinijeti boljoj kontroli ishoda za sve one koji spadaju u rizičnu grupu za pojavu AKI.