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Role of Neutrophil Gelatinase-Associated Lipocalin for Early Detection of Acute Kidney Linjury Before and After Cardiac Catheterization

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Abstract

Background and objectives: Acute kidney injury develops in up to 5% of the hospitalized patients and in up to 30% patients admitted in the Intensive Care Unit. The administration of contrast media can lead to a usually reversible form of acute kidney injury called contrast-induced nephropathy. The diagnosis is based on the increase in serum creatinine, which is delayed. It is necessary to identify and validate new biomarkers that allow for early and effective interventions. We assessed the acute kidney injury in patients undergoing coronary angiography by using marker that detect early kidney injury which is urinary neutrophil gelatinase-associated lipocalin in urine. **Method:** In patients attending Duhok cardiac center; we checked renal function test and urinary neutrophil gelatinase-associated lipocalin before cardiac catheterization as a baseline and then we screened serum creatinine and neutrophil gelatinase-associated lipocalin in urine after 48 hours of coronary catheterization for the early detection of acute kidney injury. After 2-4 week we repeated renal function tests. **Results:** Hypertension is the most common risk factor for contrast induced nephropathy among our participants. Twenty-one participants (11%) develop acute kidney injury. Only one patient needed hemodialysis which was among the risky group participants. Acute kidney injury was more common with those with risk factors for contrast nephropathy. Twenty subjects of those who developed acute kidney injury (95%) were diagnosed early by urinary neutrophil gelatinase-associated lipocalin test while serum creatinine was normal at first 48 hours. **Conclusions:** We concluded that urinary neutrophil gelatinase-associated lipocalin is early and sensitive marker for kidney injury in comparison with serum creatinine.

Keywords: Neutrophil gelatinase associated lipocalin; Acute kidney injury; Angiography.

Introduction

Acute kidney injury (AKI) is responsible for high in-hospital mortality worldwide. Early diagnosing and treatment can significantly prevent its complication and progression to chronic kidney disease (CKD). Early recognition of AKI, especially iatrogenic injury, and reversing its course is critical in emergency medicine. Mortality from AKI is estimated to be two million lives a year and those who survive AKI may have higher risk for the development of CKD[1].

Acute kidney injury commonly complicates coronary angiography with further increases in the burden on patient prognosis through increasing hospital stay and increasing mortality rate[2, 3].

In critically ill patient, subtle elevation in renal function might be associated with adverse outcome. Acute kidney injury is diagnosed by measuring serum creatinine and estimating urine flow rate. However, serum creatinine is insensitive and unreliable in diagnosing renal tubular injury in the absence of significant reduction in glomerular filtration rate (GFR)[4].

A serum creatinine elevation is noticed only when GFR has already reduced below 50% of normal rate. Therefore, more reliable biomarkers, than creatinine, are needed for an accurate evaluation of renal function and an early detection of AKI.

There are many accurate biomarkers for early detection of AKI such as cystatin-C, neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-b-glucosaminidase, liver-type fatty acid binding protein (L-FABP), kidney injury molecule-1 (KIM-1), Na+/H + exchanger isoform-3 (NHE-3), Interleukin-18 (IL-18) etc. Among these, only

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for cystatin-C and NGAL, reliable and automated assay methods are commercially available[5].

Neutrophil gelatinase-associated lipocalin is one of the biological substances which are produced by injured tubular cells and are association with immune response. Neutrophil gelatinase-associated lipocalin decreases renal tubular injury by reducing apoptosis and increasing the normal proliferation of kidney tubule cells. It also acts as growth factor and it was found to have a renoprotective effect in acute ischemic renal injury in an animal model[6].

Neutrophil gelatinase-associated lipocalin measurement (in plasma and urine) is useful for the early detection of AKI as supported by many clinical trials This helps timely diagnose and early treatment of AKI in many clinical situation like intensive care unit , cardiac care units and radio-contrast procedures[7, 8] and cardiopulmonary bypass[9].

In addition to the benefit of NGAL in early diagnosis of AKI, it is used for distinguishing pre-renal from renal AKI[10], monitoring disease activity like in lupus nephritis[11], IgA nephropathy[12], Adult polycystic kidney disease APKD[13], and diagnosis of delay graft function after kidney transplantation[14].

Neutrophil gelatinase-associated lipocalin is considered a reliable diagnostic and prognostic marker as reviewed in several systematic reviews and studies[15-18].

Our aim in this study is to evaluate the sensitivity and specificity of uNGAL for early detection of AKI[19].

Patients and methods

We recruited 192 patients admitted between January 2017 to September 2017 to Duhok cardiac center who underwent cardiac angiography with or without angioplasty. Baseline serum creatinine were measured, then we monitored participants through checking serum creatinine and urinary NGAL within 6 hours, 48 hours, one week, and four weeks from cardiac catheterization. Information were collected from the participants including age, sex, comorbidities, medications, urine output, type of intervention, precautious procedures, hospital stay and volume of the contrast used.

Precautious measures used for hospitalized participants to try to prevent AKI, including intravenous normal saline, sodium bicarbonate. We excluded those patients who were on hemodialysis, or had renal transplant and acute renal failure. Definition of AKI based on RIFLE criteria and KDIGO guideline as follow:

Acute kidney injury is defined as any of the following (Not Graded) 19, 20: increase in SCr by $\geqslant$0.3 mg/dl ($\geqslant$26.5 µmol/l) within 48 hours; or increase in SCr to $\geqslant$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours.

Evaluation of urinary NGAL was done by using ELISA kit from BioTek (Epson, ELx 800) and according to instructions of manufacturer performed.

In our study, consent was taken from all participants after explaining the nature of our study. The study methodology was approved by scientific committee of Kurdistan Board for Medical Specialties.

We analyzed the result using SSPS (version 17). We used the student›s t-test for comparing the means. A p-value of $\leq$0.05 in the final analyses was considered statistically significant.

Results

We recruited 192 patients in this study, 94 participants (49%) were male. The mean age of the patients was 63.1± 13.2 years. Hypertension was the most common risk factor for AKI post cardiac catheterization followed by diabetes mellitus in study population, Table 1. Patients attending both elective and emergency catheterization were involved in this study. Interventions included diagnostic and therapeutic angiography. The mean volume of contrast used for intervention was 68.5 milliliters. Participants characteristic were summarized in Table 1.

Table (1): Characteristics of study population.

Characteristic	No. (%)
Male	94 (49)
Female	98 (51)
BMI	27± 5.3
Risk Factor	137 (71)
Age (Mean)	63.1± 13.2
Hypertension	99 (52)
Diabetes Mellitus	83 (43)
Heart failure	14 (7)
Chronic kidney disease	6 (3)
Diuretic use	33(17)
Multiple Myeloma	0
Anemia	8 (4)
Age above 75	6 (3)
Type of intervention	
Elective catheterization	154 (80)
Emergency catheterization	38 (20)
Diagnostic catheterization	150 (78)
Therapeutic catheterization	42 (22)
Use of Precautious measures	39 (20)
Hospital stay	41 (21)
Death	0 (0)
AKI	21 (11)
Volume of contrast (Mean)	68.5

Twenty one participants developed AKI, nineteen among risky group and two with no risk factors, Table 2. No deaths were reported in in our study. Only one patient needed hemodialysis which was among the risky group participants.

Table (2): Characteristic of participants who developed AKI.

Participants who developed AKI	No. (%)
With risk factor	19 (90.5)
Without risk factor	2 (9.5)
Elective catheterization	7 (33)
Emergency catheterization	14 (67)
Diagnostic catheterization	6 (28.5)
Therapeutic catheterization	15 (71.5)
Contrast less than 50 ml	5 (24)
Contrast more than 50 ml	16 (76)
Male	5 (24)
Female	16 (76)

In our study; we found that AKI was seen more with those with risk factors, emergency catheterization, therapeutic catheterization, those received more than 50 milliliter contrast and female participants as shown in Table 2. Those without risk factor who developed AKI were obese (BMI =29), female and were on diuretics. Acute kidney injury was commoner among therapeutic catheterization as they had more risk factors and contrast volume was more than diagnostic test (Mean 112 milliliter), Table 3. Figure 1 show the time of diagnosis AKI according to serum creatinine and uNGAL

In AKI group Diabetes mellitus appeared to be highly associated with the development of AKI in our study.

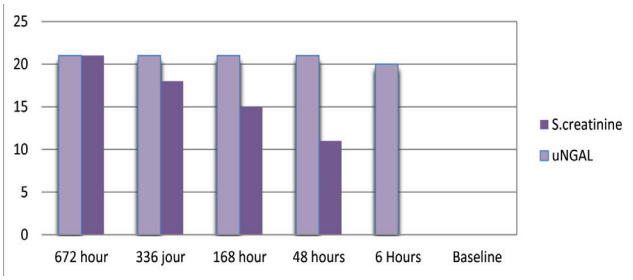

Figure (1): Pearson correlation of uNGAL and S. Creatinine.

Among those who developed AKI, twenty of them (95%) were diagnosed early by urinary NGAL test while serum creatinines were normal at first 48 hours. Serum creatinine needed at least 96 hours to increase among AKI patients. Baseline serum creatinine and uGAL were normal in those who develop AKI (with or without risk factors). Urinary NGAL was significantly different between those who developed AKI and those who did not (P value <0.001) as shown in table 3. A significant difference in urinary NGAL (P<.001) were observed between patients with risky group and the non-risky group especially within six hours from cardiac intervention as shown in Table 3.

Table (3): Comparison between AKI and Non-AKI patients.

Variables	AKI	Non-AKI	P-value
Male	5	89	0.007
Female	16	82	0.01
Age (Mean)	61.5 ± 2.9	58.2 ± 4.1	<0.001
DM	15	68	<0.05
HT	8	91	0.4482
BMI	27.8 ± 2.9	26.2 ± 1.5	0.01520
Serum Creatinine (Mean)	1.47± 0.9	1.03± 0.6	0.03
uNGAL	68 ± 18.3	32 ± 4.7	<0.001
Precautious measures	1	38	<0.05

Discussion

In the last decade, many studies tried to evaluate

biomarkers for early detection of AKI which may facilitate management of AKI in procedures associated with contrast nephropathy.

The aim of this prospective study was to evaluate whether urinary NGAL can detect AKI earlier than depending on RIFLE and KDIGO guideline criteria for diagnosis of AKI, and whether NGAL can predict the need for renal replacement therapy.

It is important to diagnose AKI as early as possible post cardiac interventions by a test that has high sensitivity and specificity. Serum creatinine is an inadequate marker for AKI because a substantial loss of glomerular filtration rate occurs before serum creatinine increment can be measured. Additionally, serum creatinine does not accurately predict renal function unless it reaches a steady state after several days[21]. Many new biomarkers are available nowadays, in many studies. NGAL appears to be one of promising markers but its usefulness likely to be when combined with other markers such as KIM-1 or cystatin C to form an "AKI panel[24].

In cardiorenal syndrome including those with acute or chronic heart failure, NGAL found to be useful as diagnostic and prognostic biomarker[25].

In this study, we tried to evaluate the usefulness of uNGAL for early detection of AKI (within 6 hours of intervention) among adult patients in need for coronary angiography with or without angioplasty.

NGAL has extremely high sensitivity and specificity for early detection of AKI following cardiac intervention in the first few days9. We used uNGAL as it has more predictive value than serum NGAL[22, 23]. Our study demonstrated that uNGAL is specific for early diagnosis of AKI in patients undergoing coronary angiography, with a higher predictive value which was also observed in study by Torregrosa et al[26]. In agreement with this, Hirsch et al reported that elevation of NGAL in serum and urine of children, who underwent a cardiac catheterization using contrast medium, can be the predictive factor to contrast induced AKI[27].

Although the commonest risk factor in our study was hypertension, AKI occurred more frequently among diabetic patients (18%) compared to the other risk factors.

Precautious measure is critical in prevention of AKI in those with high risk for kidney injury post cardiac intervention. Physiological saline used as type of hydration as a precautious measure in our study, which showed statistical significant reduction of contrast induced AKI, this benefit was seen in study done by Jarocka et al[28].

We compared the sensitivity of uNGAL to serum creatinine levels. It was found that monitoring of uNGAL provide very early warning to critical care providers[29]. More studies are needed to confirm these results and to consider measuring NGAL in clinical practice.

Conclusions

In this prospective study we concluded that uNGAL is early and sensitive marker for kidney injury in comparison with serum creatinine and urine output depends on RIFLE and KDIGO guideline. Urinary NGAL allow applying reno-protective ways and measures to identify risky patients and treating them.

We recommend a larger study and evaluating further marker for early detection of AKI. Also we need to evaluate these markers in AKI in cardiac surgery.

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