ORIGINAL ARTICLE

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The Association Between Contrast-induced Acute Kidney Injury and Neutrophil Gelatinase-associated Lipocalin

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Abstract

Objective: Neutrophil gelatinase-associated lipocalin (NGAL) has been reported as an useful marker to detect early contrast-induced acute kidney injury (CI-AKI). However most of the studies were performed in subjects taking intraarterial contrast. We aimed to evaluate the role of serum NGAL for detection of CI-AKI in patients undergoing contrast-enhanced computed tomography (CT).

Methods: We prospectively enrolled consecutive hospitalized patients with estimated glomerular filtration rate ≥15 mL/min/1.73m^2 undergoing contrast enhanced CT. Blood samples were taken before (baseline) and after 4 hours following procedure for NGAL and for serum creatinine (SCr) 12-24 hours prior to CT and again 48 hours after administration of contrast agent. The primary outcome of the study was the development of CI-AKI.

Results: A total of 70 (male, 50%) subjects with a mean age of 61.1±16.1 years were enrolled. The mean baseline SCr was 1.02±0.39mg/dL. The incidence of CI-AKI was 5.7%. In the whole group serum NGAL decreased from median 119.7 (IQR, 126.3) ng/mL at baseline to median 87.3 (interquartile range, 72.9) ng/mL after contrast application. Subjects were classified into those with and without CI-AKI. Subjects with CI-AKI did not differ in baseline demographics, renal function, presence of systemic disorders and serum NGAL levels (baseline and 4 h) compared with those without CI-AKI.

Conclusion: In conclusion, 4 h measurement of serum NGAL does not seem a useful marker for the early detection of CI-AKI following IV contrast administration.

Keywords: Neutrophil gelatinase-associated lipocalin, contrast-induced acute kidney injury, contrast-enhanced computed tomography

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) also known as contrast induced nephropathy has become the third leading cause of hospital acquired AKI, because of an increasing number of patients receiving intravascular injection of iodinated contrast media every year worldwide (1). Serum creatinine (SCr) poorly reflects early changes in glomerular filtration and defines AKI before 24-48 hours (2) so considerable effort has been put into the search for new biomarkers as early indicators of AKI (3). One of the promising biomarker is neutrophil gelatinase-associated lipocalin (NGAL).

Although renal complications associated with intraarterial contrast administration have been reported mostly, there are few studies that examined the adverse oucomes of intravenous (IV) contrast administration after computed tomography (CT) procedures.

In our study, we aimed to determine the frequency of CI-AKI among patients who underwent an IV contrast-enhanced CT and to evaluate the role of serum NGAL for detection of CI-AKI.

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METHODS

Consecutive hospitalized patients undergoing elective CT with IV contrast administration at our institution between August 2012 and March 2014 were prospectively enrolled. Exclusion criteria were age <18 years; estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, administration of iodinated contrast media within 7 days prior to study entry; history of anaphylaxis to iodinated contrast agent; lactation; evidence of acute kidney injury defined according to the Kidney Disease Improving Global Outcomes (2); acute myocardial infarction; administration of dopamine, mannitol or theophylline prior to procedure.

Demographic and clinical data were collected from patient files. These include age, gender, weight, relevant co-morbidities such as diabetes mellitus, hypertension, coronary artery disease and malignancy, current antihypertensive medications, diuretic usage. Pre and post procedure prophylaxes based on hydration and n-acetylcysteine (NAC) therapy were done according to the decision of the physician who followed up the patients.

Blood samples were obtained for SCr from all patients 12-24 hours prior to CT and again 48 h post-procedure. SCr was measured using the creatinine enzymatic assay (Jaffe ratemethod) in the Abbott C8000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA). eGFR was calculated by using (Chronic Kidney Disease (CKD) - Epidemiology Collaboration) formula (4)

Blood samples for NGAL evaluations were collected as baseline (within 1 h prior to CT imaging) and 4 h after CT imaging in ethylenediaminetetraacetic acid-anticoagulated tubes and centrifugation was carried out at 4500 cycles per minute for 10 minutes. The supernatant was separated and stored at -80°C until assayed. On study time after the samples dissolved at room temperature, NGAL levels were measured by the enzyme-linked immunosorbent assay (ELISA) technique, by using ELISA kit (Human Lipocalin-2/NGAL ELISA, number: RD191102200R @ BioVendor, Czech Republic). Subjects underwent contrast-enhanced CT were administrated of iopamidol (Iopamiro®, Santa Farma, Turkey) or iopromide (Ultravist®, Bayer, United States) (300 mg of iodine per milliliter, nonionic, monomeric, low osmolality) at doses of 1 mL per kilogram of body weight.

The primary outcome of the study was the development of CI-AKI by a rise in SCr of ≥0.5 mg/dL or a ≥25% increase from baseline value, assessed at 48 hours after a radiological procedure. This is the most widely used definition of CI-AKI in the literature (5).

The protocol was approved by the Ethics Committee of Cerrahpasa Medical Faculty (number: 16285, date: 11.06.2012). The study was performed in adherence to the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Data were expressed as mean ± standard deviation, median, interquartile range (IQR) and frequency. Data distribution was analysed with the Kolmogorov-Smirnov test. Comparison of different parameters were done using Mann-Whitney U test whereas chi-square test or Fisher's exact test was used for categorical variables. The SPSS version of 22.0 for Windows software was used for analyses. Two tailed p value <0.05 was considered statistically significant.

RESULTS

Seventy-five patients were recruited and consented, however 5 patients did not have follow-up blood testing for SCr. A total of 70 (male, 50%) subjects with a mean age of 61.1±16.1 years were enrolled. 24.3% of patients were diabetics, 40% had hypertension, 20% had malignacies, 24.3% had a history of coronary heart disease and 45.7% had infectious diseases. The mean baseline SCr was 1.02±0.39 and the mean baseline eGFR was 76.7±30.9 mL/min/1.73 m^2. Forty-eight of 70 subjects (68.6%) had a baseline eGFR of ≥60 mL/min/1.73 m^2. The hydration and NAC therapy according to patient's status and clinician's decision were given to 61.4% and 47.1% of patients, respectively. The incidence of CI-AKI was 5.7%. Baseline demographic and clinical data of the study subjects grouped based on eGFR as <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2 are shown in Table 1. Patients with eGFR as <60 mL/min/1.73 m^2 received significantly more hydration therapy before contrast procedure and used significantly more diuretic drugs than patients with eGFR as ≥60 mL/min/1.73 m^2.

In the whole group serum NGAL decreased from median 119.7 (IQR, 126.3) ng/mL at baseline to median 87.3 (IQR, 72.9) after contrast application. Twenty-six patients (37.1%) had a rise [median: 14.3 (IQR,34.7) ng/mL] in serum NGAL levels after CT imaging. For NGAL levels between baseline and after contrast exposure, we found a rise of 25% in 15 patients, a rise between 25-50% in 6 patients and a rise over 50% in 5 patients. In Figure 1 serum NGAL levels at baseline and 4 h with diagnosis of CI-AKI is shown as a logarithmic scale.

Based on the primary outcome, subjects were classified into those with and without CI-AKI. Then we compared demographic characteristics (age, gender, weight), baseline renal function, presence of systemic disorders and serum NGAL levels (baseline and 4 h) between patients with CI-AKI (n=4) and patients

Table 1. Baseline characteristics and demographic data according to baseline estimated glomerular filtration rate levels of patients undergoing contrast-enhanced computed tomography

Variable	All Patients n=70	eGFR <60 mL/min/1.73 m^2 n=22	eGFR ≥60 mL/min/1.73 m^2 n=48	p value
Age, year	61.1±16.1	72.9±9.3	55.7±15.8	0.000
Male, n (%)	35 (50)	8 (36.4)	27 (56.3)	0.122
Weight, kg	70.2±13.6	73.5±16.7	68.8±11.8	0.183
Diabetes mellitus, n (%)	17 (24.3)	7 (31.8)	10 (20.8)	0.320
Hypertension, n (%)	28 (40)	12 (54.5)	16 (33.3)	0.093
Coronary artery disease, n (%)	17 (24.3)	8 (36.4)	9 (18.8)	0.111
Malignancy, n (%)	14 (20)	5 (22.7)	9 (18.8)	0.699
Infectious diseases, n (%)	32 (45.7)	11 (50)	21 (43.8)	0.626
ACE inh/ARBs usage, n (%)	11 (15.7)	4 (18.2)	7 (14.6)	0.701
Diuretic usage, n (%)	15 (21.4)	9 (40.9)	6 (12.5)	0.007
Hydration therapy, n (%)	43 (61.4)	19 (86.4)	24 (50)	0.004
NAC therapy, n (%)	33 (47.1)	14 (63.6)	19 (39.6)	0.061
$eGFR_{baseline}$, mL/min/1.73 m^2	76.7±30.9	42.4±10.8	92.5±23.4	0.000
$SCr_{baseline}$, mg/dL	1.02±0.39	1.44±0.34	0.82±0.24	0.000
$NGAL_{baseline}$, ng/mL	119.7 (126.3)	120.9 (111.9)	113.9 (162.8)	0.548
SCr 48 h, mg/dL	0.96±0.39	1.36±0.34	0.88±0.24	0.000
NGAL 4 h, ng/mL	87.3 (72.9)	100.6 (62.5)	86.6 (113.3)	0.752
Acute kidney injury, n (%)	4 (5.7)	2 (9.1)	2 (4.2)	0.585

ACE inh: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptor blockers, NAC: N-acetyl cysteine, eGFR: Estimated glomerular filtration rate, SCr: Serum creatinine, NGAL: Neutrophil gelatinase-associated lipocalin

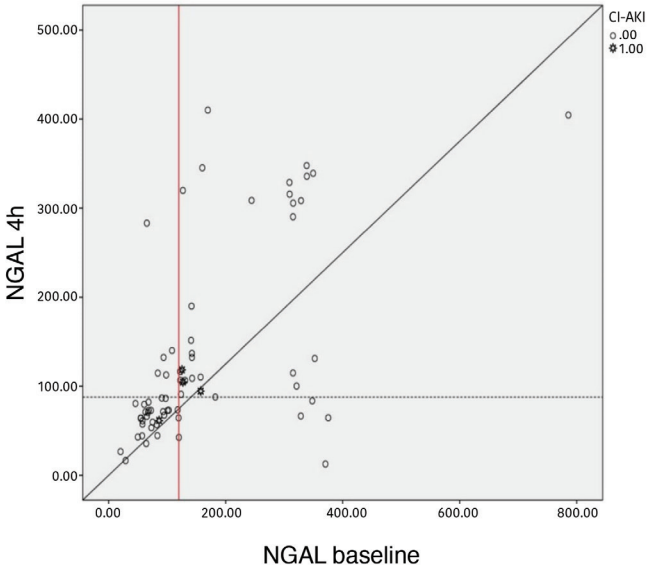

Figure 1. NGAL and CI-AKI diagnosis on a logarithmic scale. Dotted line: median level of serum NGAL 4 h, red line: Median level of baseline serum NGAL

NGAL: Neutrophil gelatinase-associated lipocalin, CI-AKI: Contrast-induced acute kidney injury

without CI-AKI (n=66). No significant differences were noted in studied variables (data were not shown). In Table 2, association of baseline serum NGAL levels with clinical variables was shown. Baseline serum NGAL was not found significantly associated with any clinical variable.

DISCUSSION

The frequency of CI-AKI in our patients undergoing IV contrast-enhanced tomography was 5.7%. The reported frequency of CI-AKI is 1-2% in patients with normal renal function, but increases up to 25% in patients with risk factors for instance the combination of CKD and diabetes, congestive heart failure, advanced age, and concurrent use of nephrotoxic drugs (6). By contrast to that associated with angiography, the risk of CI-AKI associated with contrast enhanced CT scans is quite low, even among patients with CKD (7,8). Filiopoulos et al. (9) found CI-AKI in four subjects (8.5%) in a population who underwent contrast enhanced CT and had well-preserved renal function. In another study, Weisbord et al. (8) found the frequency of AKI as 3.5% in patients with eGFR less than 60 mL/min/1.73m^2 undergoing elective contrast-enhanced CT. In addition three recent

Table 2. Association of baseline serum NGAL levels with clinical variables

Variable	Baseline NGAL (ng/mL) Median (IQR)	p value
Gender		
Female	119.9 (162.2)	0.925
Male	108.3 (115.1)	
Age, years		
≤74	120.7 (130.3)	0.572
>74	118.9 (186.1)	
Diabetes mellitus		
Yes	126.8 (155.7)	0.742
No	108.3 (144.9)	
Hypertension		
Yes	120.9 (198.9)	0.514
No	110.3 (132.5)	
Coronary heart disease		
Yes	119.5 (59.1)	0.598
No	119.9 (210.1)	
Infectious diseases		
Yes	113.0 (106.5)	0.782
No	120.9 (189.1)	
Malignancy		
Yes	111.3 (105.5)	0.971
No	120.7 (159.2)	
$SCr_{baseline}$, mg/dL		
<1	113.1 (117.8)	0.348
≥1	119.7 (195.0)	
$eGFR_{baseline}$, mL/min/1.73 m^2		
<60	120.9 (111.9)	0.548
≥60	113.9 (162.8)	

NGAL: Neutrophil gelatinase-associated lipocalin, SCr: Serum creatinine, eGFR: Estimated glomerular filtration rate, IQR: Interquartile range

prospective trials involving contrast enhanced CT with eGFR less than 60 mL/min/1.73m^2 found an overall incidence of CI-AKI, of approximately 5% (10-12). Interestingly, Muratoglu et al. (13) found CI-AKI as 16.2% in their study patients with no history of any renal disorder undergoing CT with contrast.

We know that SCr is not an optimal biomarker of kidney function and a change of SCr within 48 hours after contrast media injection might result in a delay for diagnosis CI-AKI. Over 50% of kidney function must be lost before SCr begins to rise (14). Early detection of CI-AKI after contrast media exposure is important for appropriate intervention and prevention of the progress of renal impairment. So considerable effort has been put into the search for new biomarkers as early indicators of AKI.

NGAL is a 25-kDa protein produced by renal tubular cells in response to different types of injury (15). NGAL has been proved as an early, sensitive, non-invasive biomarker for AKI in different clinical settings such as in cardiac surgery (16,17), critical care (18,19), and kidney transplantation (20,21). Also it has been shown to be useful for earlier diagnosis in patients who underwent cardiac surgery and/or any procedure with intraarterial iodinated contrast material administration (22,23). In a recent meta-analysis; NGAL level has been found as a valuable renal biomarker for predicting CI-AKI in patients who undergo percutaneous coronary intervention or coronary angiography (24). However; its performance in patients undergoing contrast-enhanced CT is unclear.

Firstly Mishra et al. (25) reported a significant rise in serum and urinary NGAL in samples taken as early as 2 h after cardiopulmoner bypass surgery in children who developed acute renal injury. They also found a small but significant rise in samples taken similarly after the same procedure in children who never developed acute renal injury. The cause of this rising was believed to be the result of NGAL release in the bloodstream secondary to inflammatory activation of neutrophils. In another study, Bachorzewska-Gajewka et al. (26) also demonstrated significantly high NGAL levels in patients with CI-AKI starting 2 h (serum NGAL) or 4 h (urinary NGAL) after percutaneous coronary intervention. Similarly McCullough et al. (27) found that serum NGAL began to rise in plasma approximately 6 h after contrast exposure in paralel with a rise in SCr in subjects with eGFR <75 mL/min/1.73 m^2 who underwent non-urgent coronary angiography. Alharazy et al. (28) had reported that serum NGAL at 4 hours did not change significantly in patients with stable CKD stages 2 to 4 who underwent coronary angiography then they found significant increase in serum NGAL at 24 hours and in SCr at 48 hours. Surprisingly, in 62.9% of our patients the concentrations of serum NGAL dropped after contrast application. Similarly to our study; Ribitsch et al. (29) found that only ten patients (1.62%) undergoing intra-arterial angiography showed a significant rise of urinary NGAL and of whom one developed CI-AKI. They found decreased NGAL levels in parallel with urine osmolality so they suggested a diluting effect might be considered. According to meta-analysis recently published by Wang et al. (24), they hypothesized that the differences between these studies might be attributed to the dilution caused by adequate hydration however the hydration regimen has not been reported in most studies studies.

We know that there are major differences in patient populations, contrast volume administrated and intra-procedural

complications between the two settings; contrast-enhanced CT and percutaneous coronary interventions. In Table 3, studies evaluating performance of NGAL predicting CI-AKI in patients undergoing contrast-enhanced CT. Firstly V. Filiopoulos et al. (9) demonstrated that plasma NGAL 6 h after contrast administration appeared to be a useful biomarker in the early prediction of CI-AKI in patients undergoing contrast-enhanced CT. Also Lacquaniti et al. (15) had reported that SCr levels showed a statistically significant increase 48 hours postcontrast whereas serum and urinary NGAL were early markers with their elevations observed after only 8 hours in their patients with stable stage 3 CKD undergoing CT with administration of iomeprol (AUC=0.995 and 0.992 for serum and urine NGAL, respectively). Muratoglu et al. (13) demonstrated that serum NGAL level increased at the 6 h and decreased at the 72 h in patients undergoing contrast-enhanced with CI-AKI (AUC=0.98). Our findings contrast these findings.

One major point of this new biomarker may be the fact that only little is known about predictive pattern or cut-off value in patients with underlying several co-morbidities such as inflammation, chronic heart disease, diabetes and CKD. Several investigators discovered a significant inverse relation between NGAL and renal function defined by eGFR (30). Because of the differences in the initial renal function, there is no effective method for integrating cut-off values (24). Ribitsch et al. (29) showed in their cohort that baseline urine NGAL levels were significantly associated with diabetes, lower GFR, cystatin C, proteinuria , age and female sex. However in our study, we did not find any association with baseline serum NGAL level and clinical variables.

Our study had some limitations. An important limitation is few sample size and the very few cases with CI-AKI (n=4). A larger study population could make the results more reliable. According to previous studies as indicated before, mostly plasma NGAL appeared to be no sooner than 4 h after contrast exposure so serial mesurements would have been valuable. A large number of CI-AKI cases will be needed with blood NGAL mesurements to determine the risk.

CONCLUSION

In conclusion, 4 h measurement of serum NGAL does not seem a useful marker for the early detection of CI-AKI following IV contrast administration.

Ethics

Ethics Committee Approval: Ethics Committee of Cerrahpasa Medical Faculty (number: 16285, date: 11.06.2012).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ., İ.M.B., Concept: E.İ., M.O., N.S., Design: E.İ., M.O., S.A., N.S., Data Collection or Processing: E.İ., İ.M.B., N.S., Analysis or Interpretation: E.İ., M.O., S.T., N.S., Literature Search: E.İ., M.O., S.A., S.T., N.S., Writing: E.İ., M.O., S.A., S.T., N.S.

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