

CAN NGAL BE USED AS AN EARLY MARKER OF CONTRAST-INDUCED NEPHROPATHY IN EMERGENCY DEPARTMENT

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ABSTRACT

Aim: The objective of this study was to indicate the importance of the level of Neutrophil Gelatinase-Associated Lipocalin (NGAL) against Serum Creatinine (SCr) for the early diagnosis of acute renal failure (ARF) related to contrast agent.

Methods: 60 voluntary patients admitted to the emergency department for various reasons who had underwent contrast-enhanced computerized tomography scans were included in the study. Blood samples for NGAL, creatinine were taken from the peripheral veins of the patients; pre exposure (0 hours) and post exposure to contrast agent on the 4th and 24th hours were examined for contrast computed tomography.

Results: NGAL value was measured 4 hours after the administration of the contrast agent in our study and was significantly increased ($p < 0.05$), however the creatinine value did not show a statistically significant change ($p > 0.05$). When NGAL values were considered in relation to age, a significant increase was observed in patients over sixty years of age ($p < 0.05$). There was no statistically significant difference between the groups based on the creatinine values ($p > 0.05$).

Conclusion: It was determined in the present study that NGAL indicates more significant results in comparison with creatinine with regard to the early diagnosis of contrast-induced nephropathy which can develop in patients who underwent a contrast-enhanced tomography scan. It is believed that NGAL can be the reagent which replaces creatinine in future studies for the early diagnosis of contrast-induced nephropathy particularly for patients aged 60 and above. Further investigations are required for clarifying the role of NGAL values in the early diagnosis of Contrast-Induced Nephropathy after contrast-enhanced computed tomography in Emergency Department.

Keywords: acute renal failure, computerized tomography, contrast-induced nephropathy, Neutrophil Gelatinase-Associated Lipocalin (NGAL).

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Introduction

Radiocontrast agents are among important reasons for nephrotoxic acute renal failure (ARF). ARF is defined as an increase in the serum creatinine value at the earliest after 24 hours following the loss of at least 50% of renal functions, incompetence to remove the final product of the metabolism from the body and an imbalance of water and electrolyte.

Neutrophilic gelatinase-associated lipocalin (NGAL) is a new biodiagnostic beginning to be used in the early stage diagnosis of acute renal injury. The objective of this study was to define Contrast-Induced Nephropathy (CIN) with NGAL at an early stage. ARF is described as the inability to release the final metabolic product from body due to failure in kidney functions in addition to a limp of water and electrolyte balance⁽¹⁾.

Radio-contrast agents are one of the most important causes of nephrotoxic ARF. They can cause damage by creating severe vasoconstriction or by direct cytotoxic effect. This matter has gained more importance in recent years as radiological imaging systems became more widespread.

ARF is an important cause of morbidity and mortality for emergency medicine. ARF is diagnosed by ED doctors. The most important diagnostic test of ARF is still the serum creatinine (SCr) value⁽²⁾. Diagnosis and treatment of ARF in ED can be delayed for many reasons; the earliest ARF diagnosis by SCr value can be made in 24 hours, SCr is not a bedside diagnosis test, there is a significant dependence on the laboratory, the results can be received in approximately 60 to 90 minutes and there are many factors that affect SCr value.

Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, interleukin-18, N-acetyl- β -d-glucosaminidase, Netrin-1 and monocyte chemoattractant protein-1 are the new diagnosis methods of ARF⁽³⁾. The objective of this study was to investigate and compare with SCr the efficacy of NGAL values for early diagnosis of Contrast-Induced Nephropathy After contrast-enhanced computed tomography in Emergency Department.

Inclusion and exclusion criteria

Sixty voluntary patients admitted to the ED for various reasons who underwent contrast-enhanced computerized tomography scan were included in the study.

Those with renal failure, pregnant, lactating mothers, thyroid sufferers, allergic to contrast agents, aged under 17 and those who were generally in bad condition or who had no stable vital signs were excluded.

Material and methods

The study was carried out at the Afyon Kocatepe University (AKU) Medical Faculty Training and Research Hospital Emergency Department between June 2013 and June 2014. This prospective clinical study included 60 consecutive, randomized patients who applied to the Department of Emergency Medicine, AKU, with traumatic or atraumatic abdominal or chest pains and who underwent contrast-enhanced abdominal and thoracic tomography scan. Sixty patients were included in the study. Ten patients were excluded because of measurement errors.

Data for 50 patients with complete blood samples from basal and radio-contrast agent application were evaluated. Of the 50 patients included, 26 (52%) were male and 24 (48%) were female.

Healthy volunteers were informed about the study protocol prior to the study and written consent was obtained from all participants. The study protocol was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Ethics Committee of AKU, Faculty of Medicine.

The study was started following the approval of AKU Ethics Committee dated 15.08.2013 and numbered 2013/10-66. It was carried out as a randomized controlled trial.

Biochemical analysis

1 cc blood sample was drawn into syringe for each patient prior to administering the contrast agent (0th hour) and on 4th and 24th hours after its injection from peripheral vascular access to slender laboratory tube for kidney function tests and to the hemogram tube with EDTA for NGAL value. Tube BUN and Creatinine values were examined in the laboratory (on cobas 6000 Roche Hitachi Analyzer, North America).

1.5 mL/kg iohexol (omnipaque 300; Amersham Health IDA Business Park Carrigtohill Co. Cork, Ireland) was injected via peripheral vein in accordance with the Radiology Department protocol prior to the tomography scan to patients with no contraindication for the contrast agent.

0.25 cc blood sample was injected to NGAL kit's chamber (Triage® brand Biosite® Inc., USA; Savas Medikal Lab. Malz. Tic. Ltd. Sti., Istanbul-Turkey) for the NGAL level after which it was waited until full distribution was achieved in micro channels. The kit was placed into the NGAL meter. NGAL level was measured automatically via fluoroimmunoassay method. The NGAL value appeared digitally on the device display in approximately 10-12 minutes after which the results were registered and printed on paper. The blood taken into the biochemistry tube routinely was examined in laboratory. Venous blood samples were taken from patients on the 0th, 4th and 24th hours after they underwent contrast-enhanced computerized tomography scan. NGAL, blood urea nitrogen (BUN) and Creatinine values of the blood were examined. 3000 cc/24h, 0.9% NaCl was administered to the patients before and after the contrast-enhanced tomography scan.

Statistical Methods

The data collected from the study was evaluated via Statistical Package Software for Social Science for Windows Version 16.0 (SPSS 16.0 Inc: Chicago.11.USA). Average values of variables and standard deviation values were calculated. Independent samples t-test was used for kidney function tests (BUN, creatinine) and for comparing NGAL values according to sex and age variables. The differences between the 0th, 4th and 24th hour evaluation values with regard to NGAL, Creatinine and BUN were tested with analysis of variance (ANOVA) for repeated measures. Bonferroni (Post Hoc) test which is one of the multiple comparison tests was used in consequence of analysis of variance, for paired comparison of ensemble average. Statistical significance value was acknowledged as $p < 0.05$.

Results

Complaint				
Age	Abdominal pain	Thoracic trauma	Abdominal trauma	Total
< 60 y	16(%43.3)	10(%27.0)	11(%29.7)	37(%100)
> 60 y	9(%69.2)	2(%15.4)	2(15.4)	13(%100)
Female	12(%46.1)	6(%23.1)	8(%30.8)	26(%100)
Male	13(%54.2)	6(%25)	5(%20.8)	24(%100)
total	50	24	26	100

Table 1: Distribution of patients as age, sex and complaint status for contrasted CT indications.

Analysis of variance results for 0th, 4th and 24th hour BUN, Creatinine and NGAL value comparison were put forth in table 2.

	Hours	n	Average	F	p
BUN	0	50	15.82±5.93	50.531	0.001*
	4	50	14.78 ±5.95		
	24	50	13.71±5.26		
Creatinine	0	50	0.742±0.21	1.697	0.19
	4	50	0.714±0.19		
	24	50	0.706±0.2		
NGAL	0	50	133.50 ±146.15	7.66	0.001*
	4	50	147.94 ±165.75		
	24	50	136.86 ±129.67		

Table 2: Analysis of variance results for 0th, 4th and 24th hour BUN, Creatinine and NGAL value comparison was obtained ($p < 0.005$).

* $p < 0.005$

A statistically significant difference was determined for NGAL values between 0 and 4th hours. The NGAL values decreased on the 24th hour. ($p < 0,05$). A statistically significant difference was determined for BUN values between 0 and 4 th hours. A statistically significant difference was determined for BUN values between 0 and 24 th hours, but the difference was not statistically significant for the 4 th and 24 th hours.

A statistically significant difference was determined between NGAL values in the 0th, 4th, 24th hours according to gender. The average value was observed as 142.11 in the 0th hour, as 160.19 in the 4th hour and as 127.15 in the 24th hour. It was determined that NGAL value increased significantly in the 24th hour for males. The average value for the 0th hour was 124.16, it was 134.66 for the 4th hour and 147.37 for the 24th hour. No statistically significant difference was observed between the results for male and female ($p > 0.05$).

Creatinine values for males was observed to be higher at a statistically significantly level in comparison with those of the females as a result of the t-test carried out for comparing creatinine values in the 0th, 4th, 24th hours according to gender.

	Hours	Age (year)	n	Average	SD	T	p
BUN	0	< 60	37	13.92	4.25	3.58	0.003*
		> 60	13	21.18	6.85		
	4	< 60	37	13.18	4.43	2.82	0.013*
		> 60	13	19.34	7.43		
	24	< 60	37	12.67	4.78	2.264	0.036*
		> 60	13	16.63	5.61		
Creatinine	0	< 60	37	0.75	0.22	0.681	0.499
		> 60	13	0.7	0.14		
	4	< 60	37	0.72	0.2	0.458	0.649
		> 60	13	0.69	0.17		
	24	< 60	37	0.7	0.18	0.122	0.909
		> 60	13	0.7	0.25		
NGAL	0	< 60	37	100.59	89.79	2.879	0.006*
		> 60	13	227.15	224.03		
	4	< 60	37	106.43	77.25	3.269	0.002*
		> 60	13	266.07	271.77		
	24	< 60	37	106.64	89.92	2.997	0.004*
		> 60	13	222.84	183.24		

Table 3: Analysis of variance results for 0th, 4th and 24th hour BUN, creatinine and NGAL values with regard to the comparison according to age. ($p < 0.005$).

SD: standard deviation.

A statistically significant difference was observed between males and females ($p > 0.005$).

Table 3. Analysis of variance results for 0th, 4th and 24th hour BUN, creatinine and NGAL values with regard to the comparison according to age. ($p < 0.005$).

Discussion

Developments on genetic and molecular biology have provided new biologic reagents. These reagents can be used for the diagnosis of ARF. NGAL that is emerging after kidney ischemia is one of them. Other functions of NGAL are induction of apoptosis, inhibiting bacteria reproduction and regulating inflammatory response⁽⁵⁾. It has been shown that NGAL values increased significantly in the blood and urine following acute renal failure⁽⁶⁾. NGAL blood value increases during the first hour following renal failure regardless of its etiology^(7,8). Cardiologists generally carried out studies on (contrast induced nephropathy) CIN and nephropathy related to contrast used in angiography. CIN causes many problems in the emergency department. Contrast agent is used for various reasons in emergency departments and especially for tomography scans. SCr value should be determined prior to administering the contrast agent to elderly patients. However, this process takes approximately 1 hour and causes the patients to lose time. Tomography scan is carried out using an improper contrast substance for some patients at the first department they apply to and so they have to wait for a second contrast-enhanced scan. For these reasons it was considered that NGAL which can be used at the bedside in a short amount of time for which no laboratory and lab technician is required and which can be used for an early diagnosis of CIN is more useful as a reagent in comparison with SCr. Many studies have been carried out which put forth that NGAL increases especially in the 4th hour after the contrast is administered.

CIN is the sudden failure of kidney functions that occurs after being exposed to the contrast agent. The most important parameter for diagnosis of CIN is the SCr value. It is defined that the required period for failure of kidney is approximately 48 hours with an increase in SCr value from 0,5 mg/dl to 1 mg/dl or between 25% to 50%⁽⁹⁾.

Toxic renal injury after administration of contrast agent is another example where an increase in the synthesis and excretion of NGAL is observed. Bachórzewska-Gajewska et al. observed an increase in serum NGAL concentrations in 2-4 hours and in urine 4-8 hours following coronary surgery. A relationship was also shown between NGAL and other parameters of renal function as cystatin C, GFR and serum creatinine. On this basis, the authors reached the conclusion that NGAL may be a useful marker for the early diagnosis of acute kidney injury in patients following coronary angiography⁽¹⁰⁾.

Haase et al., conducted a meta-analysis of 19 studies from eight countries including 2538 patients, 487 (19.2%) of whom were diagnosed with ARF and for whom NGAL concentrations were evaluated as an early marker for acute renal dysfunction. One of the evaluated risk factors for ARF was the administration of intravascular contrast. Analyses have indicated a prognostic and diagnostic value of NGAL in the evaluation of acute kidney injury induced by contrast agent⁽¹¹⁾. Similarly to these studies, it was determined in our study that NGAL value increases early in contrast-enhanced tomography scan for patients who applied to the ED. A significant increase in the creatinine value was not observed during the first 24 hours in our study, however there was a significant increase in NGAL value after the first few hours.

Unfortunately, there are some limitations regarding the usefulness of NGAL for the evaluation of renal function. Age, sex, inflammation, and diseases with accompanied liver dysfunction affect NGAL concentration⁽¹²⁾. NGAL is also present in low levels in other organs such as lungs, trachea, stomach, intestine under normal physiological conditions which may limit its specificity as a marker for kidney damage.

Renal failure incidence increases with age. Accordingly, significant differences were observed in the 0th, 4th, and 24th hours for patients aged above 60 and below 60 with regard to the comparison of NGAL value with age. No statistically significant difference was determined in the 0th, 4th, and 24th hours for patients aged above 60 and below 60 with regard to SCr values. The values were observed to be close when comparing averages.

No statistically significant difference was observed between male and female NGAL values in the present study. Statistically significant differences were observed for males in creatinine values in the 0th, 4th and 24th hours.

A statistically significant difference was observed for patients aged above 60 and below 60 with regard to NGAL values when serum NGAL and creatinine values were compared with regard to age, sex and complaint. NGAL values in the 0th, 4th and 24th hours were found to be higher at statistically significant levels for patients aged 60 and above in comparison with patients aged below 60. Risk factors such as congestive heart failure, dehydration, use of nephrotoxic medicines, hypotension and hypoxia can provide a basis for CIN development for elderly patients⁽¹³⁾. The factors that provide a basis for renal failure were excluded in the present study. Nevertheless, it should be considered that nephropathy can develop with regard to the contrast agent administered to patients.

A statistically significant difference was not observed between creatinine values in the 24th hour for patients aged above and below 60. According to our study, determining NGAL values is more useful than determining Creatinine values prior to injecting contrast agent for determining the kidney functions of elderly patients. It was determined when comparing NGAL values in first 24 hours according to gender that NGAL values increased in the 4th hour for females and in the 24th hour for males. However, these changes were not statistically significant.

A statistically significant difference was observed between SCr values according to gender. SCr values increased significantly in the 0th, 4th, and 24th hours for male patients in comparison with female patients. It has been put forth in various studies that creatinine values do not vary according to gender when diagnosing ARF, but it has also been stated in some studies that being male is a risk factor. Higher risks are found for female patients in some studies^(14,15), whereas no statistically significant difference is determined between the genders and average of diagnosed nephropathy in all other studies carried out⁽¹⁶⁾. It was determined in our study that being male can be a risk factor regarding creatinine.

NGAL was subject to many studies for diagnosing nephropathy and especially contrast-induced nephropathy. Cruz et.al. have found that NGAL increases for adult patients who developing ARF in intensive care units and that ARF can be diagnosed 48 hours prior⁽¹⁷⁾. Wagener et.al. indicate that urinary NGAL increase can be risky for ARF development following heart surgery in

adults in the 3rd hour and that⁽¹⁸⁾. It has been shown in many studies related with this subject that urine and serum NGAL tests have become a standard biomarker for early diagnosis of kidney injuries and for anticipating prognosis⁽¹⁹⁾. NGAL was used in our study as well for determining whether there is a development with regard to contrast-induced nephropathy or not. As indicated by the results of our study, there is a statistically significant difference between NGAL values in the 0th, 4th and 24th hours. It can be observed upon examining the averages that NGAL values increase in the 4th hour in comparison with the 0th hour, but decreases in the 24th hour. Our results are in accordance with literature. The reason for the decrease of NGAL may be for using low osmolarity non-ionic contrast agent and for sufficiently hydrating the patients.

The results of the study carried out by Solomon R et. al show that plasma NGAL measured by rapid, standardized assay appears to be a powerful early predictive biomarker for CIN among hospitalized patients undergoing elective contrast enhanced CT. Although a growing body of evidence suggests that the incidence of CIN may be less with IV contrast administration than that reported in coronary procedures, the widespread use of contrast-enhanced CT examinations still leaves a sizeable population vulnerable to this event^(20,21). This situation gives an idea about whether nephropathy can develop or not especially for patients who had contrast-enhanced tomography scan in ED.

NGAL can replace SCr for early diagnosis of contrast-induced nephropathy in ED especially for patients aged above 60. The other advantage of NGAL over SCr is that clinicians can work bedside in a short amount of time without the need for a laboratory and even with a small amount of blood.

It was determined in the present study that NGAL value increases early in contrast-enhanced tomography scan for patients admitted to the ED. No statistically significant increase was determined in our study for the creatinine value in the first 24 hours, however a significant increase in NGAL value was observed in the first hours.

In conclusion, it can be stated that NGAL can be used instead of Cr value for patients administered with contrast agent in ED. As far as it is known, the study is the first that addresses contrast-induced nephropathy for patients who under-

went contrast-enhanced tomography scan in ED by measuring the NGAL level. Further investigations are required to clarify the role of NGAL values for early diagnosis of Contrast-Induced Nephropathy After contrast-enhanced computed tomography in Emergency Department.

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