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The Role of Neutrophil Gelatinase-Associated Lipocalin (Ngal) in the Determination of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography

Koroner Anjiyografi Yapılan Hastalarda Kontrast Madde Nefropatisini Saptamada Nötrofil Jelatinaz İlişkili Lipokalinin Yeri

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ABSTRACT

OBJECTIVE: Contrast-induced nephropathy (CIN) is the acute kidney injury developing following the administration of contrast agent after all other reasons are excluded. We aimed to determine the role of NGAL in the urine for early diagnosis of contrast-induced nephropathy, as the disorder is an important reason of acute renal failure in cases subject to cardiac catheterization clinical practice, and the frequency is increasing.

MATERIAL and METHODS: One hundred cases undergoing elective coronary angiography between the dates of January 1st 2011 and March 1st 2011 were included in the study. Urine samples of the patients were taken maximum 4 hours after the coronary angiography to check the urinary NGAL level.

RESULTS: The creatinine level had increased 25% in 8 patients at the 48th hour following angiography and this was accepted as CIN. Using a cutoff value of 100 ng/ml, urinary NGAL levels were found to elevated in these 8 patients, consisting of 6 females and 2 males. All them had hypertension (HT) by itself or with other accompanying diseases.

CONCLUSION: The CIN diagnosis can be made with the conventional method of measuring the level of creatinine in the blood 48 hours after surgery but using the urinary NGAL method can fasten the diagnosis and treatment and also can shorten hospital stays.

KEY WORDS: Radiocontrast agents, Acute kidney injury, Neutrophil gelatinase-associated lipocalin protein, Coronary angiography

ÖZ

AMAÇ: Kontrast madde nefropatisi; diğer nedenler ekarte edildikten sonra kontrast ajanın uygulanmasını takiben gelişen bir akut böbrek hasarı tablosudur. Çalışmamızda, klinik pratikte sıklığı giderek artan ve kardiyak kateterizasyon yapılan olgularda önemli bir akut böbrek yetmezliği sebebi olan kontrast madde nefropatisinin erken tanısında üriner NGAL(neutrophil gelatinase associated lipocalin)'in yerini saptamayı amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmamıza, 1 Ocak 2011 ve 1 Mart 2011 tarihleri arasında elektif koroner anjiyografi uygulanan 100 olgu dahil edildi. Hastaların üriner NGAL seviyeleri için idrar örnekleri koroner anjiyografi yapıldıktan en geç 4 saat içinde alındı.

BULGULAR: Koroner anjiyografiyi izleyen 48. saatte 8 hastanın kreatinin seviyeleri en az %25 artmıştı ve kontrast madde nefropatisi(KMN) tanısı konuldu. Bu 8 hastanın tamamında üriner NGAL değerleri kabul edilebilir sınır olan 100 ng/ml üzerindeydi.KMN gelişen hastaların 6'sı kadın ve 2'si erkekti. Tüm hastalarda hipertansiyon veya eşlik eden bir diğer kronik hastalık mevcuttu.

SONUÇ: Anjiyografi sonrası KMN tanısı konvansiyonel metodla işlemden 48 saat sonra kreatinin düzeyi bakılarak konulabilmektedir fakat üriner NGAL düzeyi bakılması tanı ve tedaviyi hızlandırabilir ve hastanede kalma süresini kısaltabilir.

ANAHTAR SÖZCÜKLER: Radyokontrast maddeler, Akut böbrek hasarı, Nötrofil jelatinaz ilişkili lipokalin, Koroner anjiyografi

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INTRODUCTION

CIN is the acute renal failure developing following the administration of contrast agent when all other reasons are excluded (1). Contrast-induced nephropathy is one of the most frequently encountered reasons of acute kidney injury (AKI). It was reported that 13% of all CIN cases occur secondary to the use of contrast agent, and CIN is the third most common reason of AKI cases occurring at the hospital (2).

Presence of renal failure before the use of contrast agent is reported as the most important risk factor. The CIN prevalence rate varies by many factors such as the structure of contrast agent, presence of diabetes mellitus (DM), diagnosis of the patient such as severe heart failure, peripheral artery disease, multiple myeloma, and atherosclerotic heart disease; advanced age, use of nephrotoxic drugs, and the volume status of the patient before and after the procedure (3). CIN is a clinical condition that can potentially be prevented. Intravenous hydration before the administration of contrast agent and using a contrast agent with low osmolality and at the smallest dose are the generally accepted measures to prevent CIN (4). No positive effect of prophylactic dialysis has been demonstrated (5).

Contrast-induced nephropathy is accepted as an important problem as it can lead to increased inpatient time, the development of acute and chronic renal failure, and requirement of renal replacement therapy (6).

Methods for the early diagnosis of CIN are sought as CIN increases cost, morbidity and mortality. Neutrophil Gelatinase-Associated Lipocalin (NGAL), being both a plasma and urinary biomarker, has attracted interest in recent studies (7).

NGAL has the structure of 25 kDa protein and it is released in the body at very low concentrations. However, when there is epithelium damage, its level can be measured (8). After cardiac catheterization, the level of NGAL could be measured in the plasma in 2 hours and in the urine in 4 hours (9).

Our aim in this study was to determine the role of NGAL in the urine for early diagnosis of contrast-induced nephropathy, as this disorder is an important reason of acute renal failure in cases subject to cardiac catheterization, the frequency of which is increasing constantly.

MATERIAL and METHODS

One-hundred cases undergoing elective coronary angiography at our Cardiology Clinic between the dates of January 1st 2011 and March 1st 2011 were included in the study. Patients with a previous history of heart failure and renal failure were not included in the study. Age, sex, body weight, comorbid diseases, drugs used, pre-coronary angiography hematocrit level, urea, creatinine, uric acid, sodium, potassium, glucose, spot urine microalbumin level and creatinine values 48 hours after coronary angiography were recorded for all cases. An increase of 0.5 mg/dl and above in the level of serum creatinine or 25% and above compared to the basal serum creatinine level within 48 hours following the exposure to contrast agent was defined as CIN without any other reason (10). All patients included for the study were clinically euvolemic. The glomerular filtration rate (GFR) of the cases was calculated with the formula of Cockcroft–Gault. The quantity of contrast agent administered during the operation was recorded. Urine samples of the patients were taken maximum 4 hours following the coronary angiography to examine the urinary NGAL level. They were kept in vortex at -80 degrees until the data collection was completed. Total blood count was performed with the Coulter counter. Other biochemical parameter levels were measured with the Olympus Au 640 ® auto analyzer. The urinary NGAL level was measured spectrophotometrically with the Abbott Diagnostics® unit and Architect® analyzer (analyzer comprises of micro particles coated with monoclonal antibody). Values 100 ng/mL and above were accepted as positive and lower values were accepted as negative (Architect Urine NGAL, Abbott Ireland Diagnostics Division)(11,12). An increase in the serum creatinine levels at least by 25%, 48 hours after angiography, compared to the pre-intervention levels was defined as contrast-induced nephropathy.

While assessing the findings of the study, the SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analyses. Correlation (Pearson) and multiple linear regression tests were used. In addition to descriptive statistical methods (average, standard deviation), Student's t-test was used for intergroup comparisons of parameters showing normal distribution while comparing the quantitative data was employed for evaluation of study data, Mann Whitney U test was employed for intergroup comparison of parameters not showing normal distribution. The Chi-square test and Fisher Exact chi-square tests were employed to compare qualitative data. The results were assessed with a confidence interval of 95% and the significance was assessed at the level of $p<0.05$. The study protocol was approved by the local ethics committee.

RESULTS

One hundred patients were included in the study. 60 (60%) of the patients were male and 40 (40%) were female. The mean age was 61.6±10 years; 29 (29%) of patients had no chronic disease, 26 (26%) had a diagnosis of hypertension, 4 (4%) had a diagnosis of DM, 1 (1%) had a the diagnosis of hyperlipidemia (HL), 11 (11%) had diagnoses of DM and hypertension, 3 (3%) had diagnoses of HL and DM, 11 (11%) patients had diagnoses of HL and hypertension, 4 (4%) had diagnoses of HL and DM and hypertension. Eleven (11%) patients had chronic diseases other than these grouped three diseases and were named as the other group.

The medication use of the patients was grouped as metformin, ACE/ARB, statins and other. We did not make a change in the medication of the patients before the intervention. Thirty-one patients (31%) did not use medicine, as there were patients with a chronic disease that did not take medicine. The number of

patients using metformin was 6 (6%), the number of patients using ACE or ARB was 18 (18%), and the number of patients using statin was 6 (6%).

The mean creatinine value of the patients was 0.97±0.2 mg/dl, and the mean hematocrit value was as 40.2±4.2%. Pre-angiography laboratory data are presented in Table I. Blood glucose levels of the cases were measured and recorded. Mean blood glucose value was 109.3 ± 36.3 mg/dl, the highest blood glucose was 276 mg/dl and the lowest was 65 mg/dl. While 22 patients had a diagnosis of DM, 5 patients not included in this group were diagnosed as DM for the first time.

Mean level of spot urine microalbuminuria was 2.2 ±4.5 mg/dl with a minimum of 0.06 mg/dl and maximum of 38.4 mg/dl. Microalbuminuria was identified in one patient where the value was 38.4 mg/dl, and the rest had values lower than 30 mg/dl. The case with microalbuminuria had DM+HT as chronic diseases and used metformin and the other group of anti-hypertensive drugs. The case whose GFR was 68 ml/min did not have contrast-induced nephropathy.

The GFR of the patients was calculated with the Cockroft-Gault formula. The mean GFR value was 92.4±28.3 ml/min with the minimum value was 41.9 ml/min and the maximum value 168.4 ml/min. The quantity of contrast agent administered during the operation was recorded. The agent used was iopamidol (Iopamiro®) non-ionic contrast agent. The average amount used was 98.1±90 ml, the minimum 30 ml and the maximum 400 ml. There was 1 patient in whom 400 ml contrast agent was administered. Contrast-induced nephropathy was not seen in the case with HT+HL where GFR was was 61.1 ml/min. The urine NGAL level was lower than the measurement limit.

The creatinine level of 8 patients at the 48th hour following angiography had increased at a rate of 25% and this was accepted as CIN. There were six females and 2 males developing CIN. Using a cutoff value of 100 ng/ml, urinary NGAL levels were elevated among these 8 patients. The mean age was 66.2±6.3 years. All 8 patients had chronic diseases. All had HT alone or with other chronic diseases. While 2 of these patients used metformin, 3 used statins and 6 used ACE or ARB group drugs. One patient used medications from the ‹other› group.

The mean GFR was calculated as 94 ml/min±39 ml/min. Spot urine microalbumin level was found to be 2.1±2.7 mg/dl. The mean quantity of contrast agent administered was recorded as 102±109 ml. Some basic data of the patients developing or not developing CIN have been presented in Table II, III.

Correlation analyses were performed to understand the relationship between urinary NGAL levels and other variables (Table IV). The variables that showed a significant association with urinary NGAL levels in correlation analyses were evaluated in multivariate (backward) analysis. Urinary NGAL positivity was an independent predictor for CIN (β= 0.901, t= 22.207, p< 0.001).

Table I: Pre-operative laboratory values of the patients.

	Mean ± SD (min-max)
Hematocrit %	40.2±4.2 (30-55)
Urea (mg/dl)	35.3±12 (15-111)
Creatinine (mg/dl)	0.9±0.2 (0.6-1.7)
Sodium (mmol/L)	138.5±3.2 (126-151)
Glucose (mg/dl)	109±36.4 (65-276)
GFR (mL/min/1.73 m^2)	92.4±28.3 (41.9-168.4)
Uric acid (mg/dl)	5.4±1.6 (0.7-10)
LDL (mg/dl)	109±36 (28-276)
HDL (mg/dl)	44±9.5 (27-75)
Spot urine microalbuminuria (mg/dl)	2.2±4.5 (0.06-38.4)

Table II: The correlation of basic demographic data with CIN.

	NO CIN n:92	**CIN** n:8	**p**
Sex	F: 34 M: 48	F: 6 M:2	p<0.05
Age	60.7±11	66.2±6.3	NS
Number of chronic disease	2.4±2.2	4.4±2.8	p<0.05
Number of drugs used	2.5±2.3	5±2.4	p<0.05

Table III: Comparison of laboratory parameters of patients with and without CIN.

	NO CIN n:92	**CIN** n:8	**p value**
Pre-operative Hematocrit %	40.3±4.3	38±3.6	NS
Pre-operation creatinine (mg/dl)	0.98±0.2	0.85±0.2	NS
Post-operation creatinine (mg/dl)	0.9±0.2	1.3±0.5	p<0.05
Uric acid (mg/dl)	5.4±1.6	5.0±2.3	NS
Post-operative GFR (ml/min)	92.3±27	94±39	NS
Glucose (mg/dl)	109±36	110±30	NS
Spot urine microalbuminuria (mg/dl)	2.2±4.6	2.1±2.7	NS
Quantity of contrast (ml)	97.7±89	102±109	NS
Patients with urinary NGAL positivity	92	8	p<0.001

Table IV: Parameters correlated with urinary NGAL positivity.

	Urinary NGAL positivity correlation
Post-operative creatinine increase	r = 0.308 p< 0.002
CIN	r = 0.930 p< 0.001
Presence of chronic disease	r = 0.196 p= 0.05
Drug use	r = 0.234 p= 0.02
Left anterior descending coronary artery lesion	r = 0.192 p=0.05
Female sex	r= 0.211 p= 0.03

DISCUSSION

AKI is a frequent cause of morbidity and mortality and these can be reduced by means of early diagnosis and proper treatment. Mishra et al. emphasize the NGAL level as a new indicator for the early diagnosis of acute renal failure (13).

NGAL can be excreted with the urine due to its small molecular size and resistance to destruction. NGAL is from the lipocalin family and it is a protein 25 kDA in weight that is bonded to gelatin in the neutrophil with a covalent bond. It is generally secreted from the kidney, trachea, liver, stomach and colon in very small quantities. NGAL secretion from the lung, colon and especially from the kidney increases in the event of epithelium damage (14). Experimental and clinical studies have shown that NGAL accumulates in the systemic and kidney pool at the early stage of acute renal damage due to many causes. Gene studies have revealed that NGAL mRNA expression increases in the thick branch rapidly and intensively in cases with acute renal damage and collects in the tubules, It is synthesized in the distal nephron and secreted to the urine. The origin of most urinary NGAL was shown in this way (15). Acute renal damage also leads to increased NGAL expression in remote organs (especially the liver). The increase of NGAL in the systemic circulation in acute renal damage may also be due to the acute phase reactants secreted by macrophages, neutrophils and other immune system components (16).

All these findings indicate that NGAL can be used as the biomarker for acute renal damage. The latest studies have shown that NGAL plays a role in contrast-agent nephropathy (17,18). Deterioration of renal function caused by radiographic contrast agents is generally light and temporary. However, it may lead to permanent dysfunction and require renal replacement therapy. Moreover, the third leading reason of renal failure developing in inpatients is contrast-induced nephropathy (2).

We found the level of urinary NGAL to be high in cases developing CIN, in harmony with the literature, when searching the role of urinary NGAL for determination of CIN among patients undergoing coronary angiography (17-19). While both urine and blood were analyzed in the literature, we analyzed the urine due to the lower cost. One of the restrictions of our study was not analyzing the levels of serum and urine NGAL in correlation (17-19). Determination of NGAL level 4 hours after the operation, before creatinine levels increase, is important for the diagnosis of CIN. Another restriction of our study is that the high levels of urinary NGAL level could not be monitored.

Similarly, by Mishra et al it has been shown that serum and urine NGAL levels taken after 2 hours from the operation increased significantly in children developing acute renal failure after cardiopulmonary bypass surgery. Controversially, the levels of NGAL were also increased in children without acute kidney injury(13). This entity was attributed to the long duration of operation and the need for extracorporeal circulation. The reason why our patients without renal injury did not have an increase in NGAL levels may be due to the short duration of coronary angiography than cardiopulmonary bypass surgery and not requiring extracorporeal circulation. Moreover, ischemia reperfusion injury might have an effect on the outcomes of the study of Mishra et al. The increase of NGAL levels after the coronary angiography may be secondary to inflammation caused by the triggered activation of neutrophils. In addition to this, NGAL might be secreted from injured atherosclerotic plaque during angiography(20).

The cases were evaluated in terms of risk factors of contrast-induced nephropathy development. A positive correlation was found between CIN and the number of chronic diseases in our study (R:+0,218, p<0.05).Mehran et al. found hypertension to be a significant risk factor in risk scoring (21). The correlation between hypertension and CIN could not be established in our study as hypertension was present by itself or with other diseases in all cases developing CIN. The reason of non-availability of statistical correlation may be because of the limited number of cases.

Whereas the correlation between CIN and DM does not constitute a certain risk factor for CIN if proteinuria, microalbuminuria and renal failure are not also present, it is stated that there may be a moderate risk increase (5-7%) (22). The presence of DM increased the risk of CIN by 5-30% in another study whereas it was only 2% among non-diabetics(23). In our study there was no correlation between the presence of DM and CIN. These patients were thought to be without overt diabetic nephropathy. There has only been one reported case with microalbuminuria. This case had DM and hypertension and the GFR was 68 ml/min but CIN was not found.

There was a positive correlation between drug use and CIN (R: +0.259 , p<0.05). ACE/ARB group drugs were used by 6 of the cases developing CIN. The most frequently used medication group in cases developing CIN was the ACE/ARB group drugs. There are various opinions on the use of ACE/ARB's in the

literature. Gupta et al. stated that they increased CIN risk (24). Dangas et al. supported this opinion in a study conducted in 2005 (25). However, Toprak et al. argued that they prevented CIN in diabetic patients but constituted a risk for non-diabetic patients (26).

The risk of CIN increases in patients 75 years old and above based on Mehran risk scoring for CIN (21). Age constitutes an independent risk factor in the literature (25,27). We did not find a significant correlation between age and CIN in our study.

The gender was associated with risk in our study ($p<0.05$). There are two different opinions related to the correlation of CIN development and sex. Mehran et al. argue that female sex increases the risk and Cochran et al. argue the opposite (21,28).

No correlation was established between the hematocrit level and CIN development, However, there are varying studies pointing out that the risk of CIN increase with higher hematocrit levels, with a possible mechanism that high hematocrit levels may cause renal medullar hypoxia(23).

Ratio of CIN was 8 % in our study, it was above the measurement limit of urinary NGAL level. 29 patients had no comorbid disease. 8 patients that CIN was diagnosed had HT. While statistically significant correlation could be established in terms of development of chronic disease and CIN, no correlation could be established with HT alone. It may be attributed to the limited number of cases.

There was a case with microalbuminuria and both DM and HT where CIN was not detected.

Various studies have shown the role of NGAL in the diagnosis and treatment of contrast-induced nephropathy (29). The CIN diagnosis can be made by the level of creatinine 48 hours later using the conventional method with blood. The increased urine CIN 4 hours after surgery accelerates the diagnosis and treatment and shortens the duration of hospitalization and is therefore useful. We believe NGAL may become an important clinical marker of acute renal injury and more extensive studies should be carried out on this subject.

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