Relationship between brain natriuretic peptide, microalbuminuria, and contrast-induced nephropathy in patients with acute coronary syndrome

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Abstract

Objective: Patients may develop kidney failure because of the contrast agent given during coronary angiography. Renal dysfunction and heart failure were previously shown to be associated with the development of contrast nephropathy. In our study, we aimed to investigate whether there is a relationship between subclinical renal (indicated by microalbuminuria) and/or cardiac (indicated by the height of the BNP) dysfunction between the development of contrast-induced nephropathy on patients undergoing angiography due to acute coronary syndrome.

Methods: This is an observational prospective cohort study. A total of 170 patients hospitalized with a diagnosis of acute coronary syndrome in the coronary care unit were included in this study. Blood samples were collected from 145 patients without microalbuminuria and 25 patients with microalbuminuria to determine their BNP levels before coronary angiography. The patients' urea and creatinine levels were examined before and 72 h after coronary angiography. Statistical analysis was performed using Kolmogorov-Smirnov test, Mann-Whitney U test, independent samples t-test and the chi-square test.

Results: The study subjects included 82 females and 88 males (average age, 64.4±14.5 years). The BNP levels and height distribution of the 145 patients without microalbuminuria were compared between those with and without contrast agent-induced nephropathy, but no significant difference was found (205.6±280.6, 198.0±310.0, p=0.817). Similarly, no relationship between the microalbumin level and contrast agent-induced nephropathy was found in 25 patients.

Conclusion: A relationship between BNP, microalbuminuria, and contrast agent-induced nephropathy was not found in patients hospitalized in a coronary care unit with a diagnosis of acute coronary syndrome who were scheduled for coronary angiography. Additional multicenter studies with larger patient groups should be conducted to obtain more data. *(Anadolu Kardiyol Derg 2014; 14: 505-10)*

Key words: acute coronary syndrome, brain natriuretic peptide, contrast agent-induced nephropathy, coronary angiography, microalbuminuria, type 2 diabetes mellitus

Introduction

Coronary angiography is considered to be the gold standard diagnostic method for directing not only the diagnosis of coronary heart disease but also the necessity of invasive treatment. A well-known complication of coronary angiography is acute renal insufficiency induced by the contrast agent. Contrast-induced nephropathy (CIN), without another etiologic cause, is defined as a 25% or 44 mmol/L (0.5 mg/dL) increase in serum creatinine within 3 days after administration of the contrast agent (1-4). The clinical presentation varies from asymptomatic to symptomatic renal failure and death. Thus, it is important to identify risk factors prior to the administration of a contrast agent. The pathophysiology of risk factors for CIN have been examined in clinical and laboratory studies. In this study, the relationship between serum brain natriuretic peptide (BNP), microalbuminuria, and CIN was studied in patients hospitalized with acute coronary syndrome (ACS) and scheduled for coronary angiography.

Methods

Study design

This observational prospective cohort study was approved by the local Ethics Committee of Bezm-i Alem Vakıf Gureba Education and Training Hospital, where the study was first

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begun. Written informed consent was obtained from the participants.

Study population

A total of 170 patients [82 female (48.2%), 88 male (51.8%), mean age 64.4±14.5 years (lowest age, 26; maximum age, 88)] hospitalized with a diagnosis of ACS which includes the criteria of ACS in ESC and AHA guidelines. Also, patients with cardiogenic shock and renal failure patients were excluded. Among the patients, 96 did not have type 2 diabetes mellitus, while 74 did.

Study protocol

Before coronary angiography, blood samples were collected from 145 patients without microalbuminuria in EDTA tubes and centrifuged to determine their BNP levels. In addition, 25 patients with microalbuminuria, which was identified as a 24-h urine protein level of 30-300 mg, took part in the study. Before and 72 h after coronary angiography, the serum creatinine and urea levels were measured in the patients with and without microalbuminuria. Patients who had CIN after coronary angiography were hydrated. The urea and creatinine levels of the patients decreased after hydration; thus, they did not require hemodialysis.

Study variables

Baseline demographic, clinical and laboratory parameters are: gender, age, additional disease (DM), BNP and microalbuminuria levels, urea, urea after contrast, Urea change rate after contrast, creatinine, creatinine after contrast, creatinine change rate after contrast.

Coronary angiography

An interventional team performed coronary angiography and PCI according to standard clinical practice via the femoral approach. The contrast dose was left to the discretion of the interventional cardiologist. All patients received a nonionic, low-osmolarity contrast agent.

Definition of CIN and method of assessment

Contrast-induced nephropathy (CIN), without another etiologic cause, is defined as a 25% or 44 mmol/L (0.5 mg/dL) increase in serum creatinine within 3 days after administration of the contrast agent. Before and 72 h after coronary angiography, the serum creatinine and urea levels were measured in the patients with and without microalbuminuria.

BNP and microalbuminuria evaluation

Before coronary angiography, blood samples were collected from 145 patients without microalbuminuria in EDTA tubes and centrifuged to determine their BNP levels. The plasma components were separated and placed in Eppendorf tubes, which were stored at -20°C. An Alere Triage BNP Test Kit (Waltham, MA, USA) was used to measure BNP. A Beckman Coulter Urinary/CSF Protein Kit (Brea, CA, USA) was used to identify urinary microalbuminuria.

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). The mean, standard deviation, frequency, and percentage values were used in descriptive statistics of the data. The distribution of variables was assessed by the Kolmogorov-Smirnov test. The Mann-Whitney U test and independent samples t-test were used for quantitative analyses of the data. The chi-square test was used for qualitative analyses of the data. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics (Table 1-3)

Baseline characteristics of the study group was shown in Table 1, 2. There are no significant difference between the different diagnosis of the groups (Table 1, 2). The average serum BNP value for the 145 patients without microalbuminuria was 199.3±304.0. The average serum BNP value for the 25 patients with microalbuminuria was 146.5±89.3. Contrast-induced nephropathy occurred in 30 of the 170 patients (17.6%). A total of 15 of the 30 patients who developed nephropathy (50%) were female; among these 30 patients, the mean age was 66.4±12.7 years. The 140 patients without nephropathy included 67 females (47.9%) and 73 males (52.1%); the mean age was 64.0±14.8 years. There was no significant difference in age and sex distribution

Table 1. Baseline diagnosis and treatments of the patients

	N	OAD	Mix-insulin	Long acting insulin + OAD	RAS blocker	CA	BB	Diuretic
Diabetes mellitus	74	60	8	6	51	10	7	16
Hypertension	90	16		5	45	25	10	20
COPD	23	6		2	4			3
Chronic ischemic heart disease	39	7	5	2	18	3	31	4
Tobacco use	98							

BB - beta blocker; CA - calcium antagonist; COPD - chronic obstructive pulmonary disease; OAD - oral antidiabetic; RAS - renine angiotensine system

between those patients who developed nephropathy (nephropathy positive) and those who did not (nephropathy negative) (p>0.05) (Table 3).

BNP and microalbuminuria levels (Table 4)

A total of 26 of the 145 patients who were screened for serum BNP had CIN. A total of 16 of the patients who developed nephropathy (61.5%) had normal BNP levels (0-100 pg/mL); the remaining 10 patients (38.5%) had high BNP levels. Fifty-nine patients without CIN had a normal BNP level (49.6%) and 60 patients (50.4%) had a high BNP level. The BNP level in patients with nephropathy was 205.6±280.6 compared to 198.0±310.0 in those patients without nephropathy.

A total of 4 of the 25 patients with microalbuminuria developed CIN. The average microalbuminuria level in patients with nephropathy was 162.9±88.9 mg, whereas the average microalbuminuria level in patients without nephropathy was 143.4±91.2 mg. The BNP values in the patients with and without nephropathy and microalbuminuria levels in the patients with and without nephropathy were not significantly different (Table 4).

Biochemical parameters in diabetic and non-diabetic patients (Table 5-7)

There was no significant difference between the pre-contrast serum urea level, post-contrast serum urea level, and post-contrast urea change rate in type 2 diabetic patients with and without CIN (p>0.05).

There was no significant difference between the serum creatinine level and post-contrast serum creatinine level in patients with and without CIN (p>0.05). The post-contrast creatinine change ratio was significantly higher in patients with CIN than in those without CIN (p<0.05).

There was no significant difference between the serum BNP and microalbuminuria levels in those type 2 diabetic patients with and without nephropathy (p>0.05) (Table 5).

The urea levels were not significantly different diabetic patients with or without CIN (p>0.05).

In non-diabetic patients, the urea level and urea change rate were significantly higher in patients with CIN than in patients without CIN (p<0.05). The creatinine levels were not significantly different between non-diabetic patients with and without CIN (p>0.05). The creatinine level and creatinine change rate were significantly higher in patients with CIN than in patients without CIN (p<0.05). Non-diabetic patients with and without CIN had BNP and microalbuminuria values that were not significantly different (p>0.05) (Table 6).

There was a significant correlation between BNP level and age, and pre- and post-contrast urea levels (p<0.05). There was no significant correlation between BNP levels and the post-contrast urea change rate, and between the pre- and post-contrast creatinine values and post-contrast creatinine change rate (p>0.05) (Table 7). There was no significant correlation between the microalbuminuria levels and age, pre- and post-contrast urea levels, post-contrast urea change rate, pre-and post-contrast creatinine levels, and post-contrast creatinine change rate (p>0.05) (Table 7). There was a significant correlation between age, pre- and post-contrast urea values, and creatinine values after contrast administration (p<0.05), but there was no significant correlation between age and the post-contrast urea change rate, pre-contrast creatinine value, and post-contrast creatinine change rate (p>0.05) (Table 7).

Table 2. The relation of the baseline diagnosis and nephropathy development

		Nephropathy				
		Positive		Negative		
		n	%	n	%	*P*
Diabetes	Yes	10	33.3%	64	45.7%	0.215
	No	20	66.7%	76	54.3%	
Hypertension	Yes	13	43.3%	77	55.0%	0.245
	No	17	56.7%	63	45.0%	
COPD	Yes	5	16.7%	18	12.9%	0.58
	No	25	83.3%	122	87.1%	
Chronic ischemic heart disease	Yes	7	23.3%	32	22.9%	0.955
	No	23	76.7%	108	77.1%	
Chi-square test; COPD - chronic obstructive pulmonary disease						

Table 3. After the administration of contrast agent, nephropathy positive and negative patients' age and sex distributions

		Positive		Negative		
		mean± /	n-%	mean± /	n-%	*P*
Sex	Female	15	50.0%	67	47.9%	0.831
	Male	15	50.0%	73	52.1%	
Age		66.4±12.7		64.0±14.8		0.613
Chi-squared test/Independent sample t test						

Table 4. BNP, microalbuminuria levels and the distribution of CIN positive and negative patients

		Positive		Negative		
		mean± /	n-%	mean± /	n-%	*P*
SBNP	Normal	16	61.5%	59	49.6%	0.269
	High	10	38.5%	60	50.4%	
BNP		205.6±280.6		198.0±310.0		0.817
Microalbuminuria		162.9±88.9		143.4±91.2		0.697
Independent sample t test / Mann-Whitney U test / chi-squared test. BNP and SBNP - brain natriuretic peptide and Seru; CIN - contrast induced nephropathy						

Discussion

In our study, we designed to evaluate the relationship between subclinical renal (indicated by microalbuminuria) and/or cardiac (indicated by the height of the BNP) dysfunction

between the development of contrast-induced nephropathy on patients undergoing angiography due to acute coronary syndrome. But we found no relationship between BNP, microalbuminuria levels and CIN.

Contrast media-induced nephropathy is one of the most important causes of acquired acute renal failure in hospitalized patients. Diagnostic and interventional cardiac catheterization procedures have increased the usage of contrast media; thus, CIN has become a frequent problem in clinical cardiology practice. A primary preventive approach to CIN is to perform a systematic review and risk classification of the patient's characteristics.

Lisstro et al. (5) classified the risk of developing CIN as low, medium, or high. Mehran et al. (6-8) created a simple risk scoring table from a 6-year study of 9726 patients that was composed of eight main criteria: hypotension, intra-aortic balloon pump, heart failure, older than 75 years, anemia, diabetes, contrast material volume, and creatinine level or estimated glomerular filtration rate (eGFR).

There were a lot of studies to determine patients developing contrast nephropathy. CIN development examined in the elderly population exposed commonly usage of the contrast agent and in patients with multi-risk factors for coronary artery disease. The elderly, heart failured patients and patients with impaired renal function have an increase incidence of CIN (9, 10). Contrast media exposure is going to increase in diabetic patients who have diabetic nephropathy and the development of CIN causes additional problems in this population. Is the risk of developing CIN in every stage of diabetic nephropathy? Here, we tried to answer this question in our study. We investigated the risk of contrast nephropathy in diabetic patients with and without microalbuminuria. We have detected that the presence of microalbuminuria is not a risk for CIN. The contrast media usage in the stage of microalbuminuria in which the kidney has no change or irreversible abnormalities on its structure, doesn't constitute a further deterioration of renal function.

The course of renal failure in patients with type 2 diabetes mellitus is heterogeneous in its features. The switch between normoalbuminuria, microalbuminuria, and macroalbuminuria in type 2 diabetes mellitus is quite variable. Approximately 20-30% of patients exhibit these structural changes at the time of diagnosis, and microalbuminuria is reversible at this stage in 5-20% of cases. Within 10 years, microalbuminuria develops into nephrotic range proteinuria in these patients. For this reason, the level of protein in the urine of patients with diabetes should be monitored. In our study, the 24-h urine protein level was measured to detect microalbuminuria. There was no significant correlation between the microalbuminuria level and age, urea level, post-contrast urea level, post-contrast urea change rate, creatinine level, post-contrast creatinine level, and post-contrast creatinine change rate ($p>0.05$).

Table 5. Values in diabetic patients with and without contrast induced nephropathy

	Positive	Negative	
DM (+)	**Avr.±s.d.**	**Avr.±s.d.**	***P***
Urea	45.0±14.0	44.9±20.7	0.420
Urea after contrast	60.9±34.3	42.8±19.1	0.079
Urea change rate after contrast	33.3%±62.7%	0.2%±32.0%	0.081
Creatinine	0.9±0.3	1.0±0.2	0.309
Creatinine after contrast	1.1±0.6	1.0±0.2	0.236
Creatinine change rate after contrast	42.9%±16.5%	0.5%±15.9%	0.000
BNP	269.4±388.9	205.7±250.8	0.786
Microalbuminuria	146.1±51.8	123.5±88.7	0.738
Mann-Whitney U test			

Table 6. Contrast values in non-diabetic patients with and without nephropathy

	Positive	Negative	
DM (-)	**Avr.±s.d.**	**Avr.±s.d.**	***P***
Urea	38.4±11.0	35.6±14.0	0.195
Urea after contrast	58.1±29.8	35.4±14.3	0.001
Urea change rate after contrast	50.2%±65.8%	1.6%±26.0%	0.000
Creatinine 0.9±0.4	0.9±0.3	0.335	
Creatinine after contrast	1.1±0.4	0.9±0.4	0.030
Creatinine change rate after contrast	37.8%±15.4%	-0.1%±13.0%	0.000
BNP	177.3±225.3	192.0±350.8	0.927
Microalbuminuria	179.8±141.1	169.8±92.8	0.901
Mann-Whitney U test. BNP - brain natriuretic peptide			

Table 7. BNP and microalbuminuria, age and correlation of values

		Age	Urea	Urea after contrast	Urea C.R. after contrast	Creatinine	Creatinine after contrast	Creatinine C.R. after contrast
BNP	r	0.374	0.285	0.215	0.041	-0.070	0.004	0.048
	p	0.000	0.001	0.010	0.626	0.402	0.965	0.568
Microalbuminuria	r	0.160	0.065	0.044	-0.046	0141	0.118	0.152
	p	0.444	0.758	0.835	0.826	0.501	0.573	0.467
Age	r	-	0.385	0.376	0.130	0.051	0.152	0.099
Pearson correlation. BNP - brain natriuretic peptide; CR - change rate								

B-type natriuretic peptides are synthesized by cardiac myocytes against increased ventricular wall stress. We decided to investigate the relation between increased BNP levels in patients with heart failure and the development of CIN and so we looked the BNP levels before the procedure. As a result, there was no difference between the BNP levels in the patients with and without CIN and in the diabetic sub-group patients. Jarai et al. (11) recently reported that BNP levels at the time of the admittance to the hospital predict the CIN development in patients with ST elevation myocardial infarction (MI). They investigated BNP levels in 979 patients with ST segment elevation before PCI and used the same parameters for the development of CIN as we did. They reported 131 patients (13.3%) who developed CIN. This was a rate close to the rate that we reported in our study (17.6%). They found correlation between BNP levels and development of CIN, unlike our study because all patients took part in the study had ST-segment elevation MI, in another word transmural MI in which the BNP levels were higher than the levels of BNP in patients who took part in our study. So in this way; we have an opinion of BNP at physiological level effects different from the increased BNP level which is an indicator of the severity of the disease. Thus, supra-physiological levels of BNP, as well as moderate elevated BNP level is not a risk for the development of CIN. There are limited studies on this subject. One of them is the study of Zhang et al. (12). They separated 149 consecutive acute myocardial infarction patients with heart failure who underwent percutaneous coronary intervention (PCI) in 2010 into a recombinant human BNP-treated (rhBNP) group and placebo group. The serum creatinine level was lower in the rhBNP group than in the control group at 24 h, 48 h, 72 h, and 7 days after PCI. The eGFR after PCI was higher in the rhBNP group than in the control group. The occurrence of CIN was significantly lower in the rhBNP group than in the control group. As a result, it is believed that the usage of BNP in patients with heart failure before primary PCI reduces the formation of CIN compared to routine treatment alone (12, 13). Very high doses of BNP had a protective effect on CIN development which was emphasized. In this study, this finding stands as the revers of the one that Jarai et al. (11) reported but in fact this can explain by the compensation mechanisms which are result of high BNP levels underlying severity of disease. Highly increased BNP is actually a bad sign of severe ventricular in patients with ST elevation MI. CIN development is more likely in this situation. Increased BNP level in the early stages of compensation provides natriuresis which is rather a useful compensation. Zhang et al. (12) reported the usefullness of additional BNP while an unimpaired myocardium exist.

In our study, there was a significant correlation between BNP level and age, urea, and post-contrast urea level ($p<0.05$). There was a significant correlation between age and the urea level, urea level after contrast administration, and creatinine level after contrast administration ($p<0.05$). BNP levels increase with age. In addition, renal function is more easily impaired by the contrast material in older patients. In the present study, the significant difference between BNP level, urea level, and post-contrast urea level may be due to age.

In this study, no association between BNP, microalbuminuria, and CIN was found in patients with ACS. A better understanding of the pathophysiology of and risk factors for CIN will aid in prevention. Numerous clinical and laboratory studies are ongoing to determine the risk factors for CIN.

Study limitations

A major limitation of our study is the number of the study group. That is why these results may not indicate a significant correlation. Thus, this study should be considered a pilot study and additional studies should be conducted in future.

Conclusion

In this study, no relationship between BNP, microalbuminuria, and contrast agent-induced nephropathy was found in patients hospitalized in a coronary care unit with a diagnosis of ACS who were scheduled for coronary angiography. Future multicenter studies with larger patient groups should be conducted to obtain more data.

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