The effects of chronic usage of enzyme inhibitors and angiotensin receptor blockers on contrast-induced nephropathy in low-risk patients

Düşük riskli hastalarda anjiyotensin dönüştürücü enzim inhibitörleri ve anjiyotensin reseptör blokerlerinin kronik kullanımının kontrast madde nefropatisi üzerine etkileri

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ABSTRACT

Objective: There is conflicting data about the role of renin- angiotensin- aldosterone system (RAAS) blockers in contrast-induced nephropathy (CIN) pathophysiology. In this study, we aimed to investigate the effects of chronic usage of RAAS blocker drugs on development of CIN in low risk patients.
Methods: Study was designed as a prospective cohort study. A total of 295 patients were enrolled in the study. Study population was consisted of three subgroups according to prior usage of RAAS blockers: no RAAS blocker group (n=95), angiotensin-converting enzyme inhibitor (ACEI) group (n=106), angiotensin receptor blocker (ARB) group (n=94). CIN was defined as an increase of ≥25% in creatinine over the baseline value or 0.5 mg/dL rise within 48-72 h of angiography. Mehran score was calculated for each patient. Baseline variables and percentage of CIN were compared with ANOVA, Mann-Whitney U, Kruskal-Wallis and Pearson Chi-square tests between groups. In order to determine the independent predictors of CIN, binary logistic regression analyses were performed.
Results: CIN occurred in 18 patients (17.0%) in the ACEI group, 17 patients (18.1%) in ARB group and 7 patients (7.4%) in the no RAAS group. CIN occurrence was significantly higher in RAAS than no RAAS group (17.5% vs. 7.4%, p=0.01). Chronic RAAS blocker administration was an independent predictor of CIN (OR=2.69; 95% CI: 1.025-7.067; p=0.04). Mehran score was the only other independent predictor for CIN (OR=1.15; 95% CI: 1.019-1.310; p=0.02).
Conclusion: In patients with near normal renal functions who are undergoing elective coronary procedure, chronic usage of ACEI and ARB increases the risk of CIN. *(Anadolu Kardiyol Derg 2013; 13: 245-50)*
Key words: Contrast-induced nephropathy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, regression analysis

ÖZET

Amaç: Kontrast madde nefropatisi (KMN) koroner girişim yapılan hastalarda önemli bir sorundur. Renin- anjiyotensin-aldosteron sistemi (RAAS) blokerlerinin KMN gelişimindeki rolüne ait veriler çelişkilidir. Bu çalışmada düşük riskli hastalarda kronik RAAS blokeri ilaç kullanımının KMN gelişimi üzerine olan etkisinin araştırılması amaçlanmıştır.
Yöntemler: Prospektif kohort olarak dizayn edilen çalışmaya elektif koroner girişim yapılan 295 hasta alındı. RAAS blokeri kullanımına göre hastalar 3 ayrı gruptan oluşturuldu: RAAS blokeri kullanmayanlar (n=95), anjiyotensin dönüştürücü enzim inhibitörü (ADEİ) kullananlar (n=106), anjiyotensin reseptör blokeri (ARB) kullananlar (n=94). KMN koroner girişim sonrası 48-72 saat içinde bazal kreatinin değerinde %25 ve üzeri veya 0.5 mg/dL artış olması şeklinde tanımlandı. Her hasta için Mehran skoru hesaplandı. Gruplar arasındaki bazal veriler ve KMN gelişimi ANOVA, Mann-Whitney U, Kruskal-Wallis ve Pearson Ki-kare testleri ile karşılaştırıldı. KMN için bağımsız öngördürücülerin bulunabilmesi için binary lojistik regresyon analizi yapıldı.
Bulgular: ADEİ grubunda 18 (%17.0), ARB grubunda 17 (%18.1), RAAS blokeri kullanmayan grupta 7 (%7.4) hastada KMN gelişti. RAAS blokeri alan grupta KMN gelişimi almayan gruba göre anlamlı olarak fazlaydı (sırasıyla %17.5 - %7.4, p=0.01). Kronik RAAS blokeri kullanımı (OR=2.69; %95 GA: 1.025-7.067; p=0.04) ve Mehran skoru (OR=1.15; %95 GA: 1.019-1.310; p=0.02) KMN için bağımsız öngördürücüler olarak bulundu.

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Sonuç: Elektif koroner girişim yapılan, normal veya normale yakın böbrek fonksiyonları olan hastalarda kronik ADEİ ve ARB kullanımı KMN gelişimi riskini arttırmaktadır. *(Anadolu Kardiyol Derg 2013; 13: 245-50)*
Anahtar kelimeler: Kontrast madde nefropatisi, anjiyotensin dönüştürücü enzim inhibitörü, anjiyotensin reseptör blokeri, regresyon analizi

Introduction

Contrast-induced nephropathy (CIN) is characterized by acute deterioration of renal functions that occurs after parenteral administration of contrast media in the absence of other possible causes of renal impairment. Its incidence varies widely due to usage of different definitions, and also different population characteristics. The most commonly used definition is an increase in serum creatinine by 25% or by 0.5 mg/dL from a baseline value by 48-72 h post contrast administration (1). In patients with normal renal functions, CIN has been reported as occurring in 3.3-14.5% of patients (2). Factors that have been identified to be associated with CIN include: diabetes mellitus, congestive heart failure, recent acute myocardial infarction, cardiogenic shock, and pre-existing renal impairment. CIN is associated with renal failure, prolonged hospitalization, increased mortality and morbidity (3). As there is no specific therapy for CIN, the main focus is on preventive strategies. Some preventive measures are well defined such as optimal hydration of the patients, avoidance of concomitant nephrotoxic drug usage and minimizing the amount of contrast media. However the role of renin-angiotensin-aldosterone system (RAAS) blocking agents, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in the pathophysiology of CIN remains controversial, as the available literature is conflicted and discordant. Some reports have implicated these RAAS blocking agents as nephrotoxic and exacerbating renal failure with CIN whereas other reports have touted the use of these same RAAS blocking agents to protect the kidneys from the effects of CIN (4-8).

Previous studies on this topic generally focused on the patients with chronic kidney disease, hemodynamic insufficiency and acute myocardial infarction (5-8). In the majority of these studies the role of continuing or withdrawing of ACEI and ARB on development of CIN were examined. However the knowledge about chronic usage of these drugs in stable patients who underwent elective cardiac angiography and intervention is limited.

In this study we aimed to investigate the effects of chronic usage of RAAS blocker drugs on development of CIN and to establish the predictors of CIN in stabile patients who underwent elective coronary angiography and intervention.

Methods

Study design

A prospective cohort study was designed.

Study population and study protocol

Study was performed in patients 18 years of age and older who were referred to our cardiology department for non-emergent coronary angiography between May 2010 and July 2012.

Study population was designed as 3 subgroups; group 1 with no RAAS blockers; group 2 patients on chronic use of ACEI and group 3; patients on chronic use of ARB. Enrolling 100 consecutive patients for each group was planned.

The patients who underwent emergent or early invasive coronary procedures (coronary procedures within initial 48 hours of acute coronary syndromes), who had hemodynamic instability, who had severe chronic renal disease (glomerular filtration rate <30 mL/min) were excluded from the study. Usage of aldosterone antagonists and other nephrotoxic drugs were also defined as exclusion criteria.

Contrast-induced nephropathy was our primary end-point and the secondary end-point was change of creatinine (delta Cre) after procedure compared to baseline value.

All of the participants gave written informed consent and the local research ethics committee had previously approved the study protocol. The patients were followed for 48-72 hours after the procedure for the assessment of renal functions. After exclusion of 33 patients who did not complete the post procedural follow-up, a total of 295 patients were enrolled in the study. Among these, 95 were in group 1 (no RAAS blocker), 106 were in group 2 (patients on ACEI) and 94 were in group 3 (patients on ARB).

Study variables and definitions

The presence of hypertension, diabetes mellitus, hyperlipidemia and history of coronary artery disease were assessed via patients' medical questioning. Blood pressure was measured according to recommendations.

Chronic RAAS blocker usage was defined as the use of the drug for a minimum of one month. No RAAS blocker group consisted of patients who did not use any RAAS blockers more than one month. Baseline and follow-up glomerular filtration rate (eGFR) were estimated using the Cockcroft-Gault formula: (140-age)*weight (kg)/serum creatinine (mg/dL)* 72 (*0.85 in female) (9). Mehran score was calculated according to assessment of the associated risk factors, including dose of contrast media, baseline eGFR, age, presence of hypotension, heart failure, anemia, and diabetes mellitus (10). As long as the study population was consisted of stabile patients, some parameters of Mehran score such as hypotension and usage of intra-aortic balloon pump were ignored. CIN defined as an increase of serum creatinine 25% over the baseline value or 0.5 mg/dL rise within 48-72 h of coronary angiography procedure (1).

Laboratory analysis

A blood sample for serum creatinine, blood urea nitrogen (BUN), glucose, albumin, total cholesterol, sodium, and hemoglobin was drawn before the angiography after an 8-hour overnight fast and follow-up serum creatinine and BUN were measured

48-72 h after angiography. Serum creatinine was determined using an auto-analyzer, enzymatically and using the Jaffé method.

Angiography and contrast media

Type and amount of contrast media used were recorded for each patient. Three types of contrast agents (ioxaglate, iodixanol and iopromide) were used for coronary procedure. According to ethical rules, the patients whose baseline creatinine was ≥1.2 mg/dL, received preventive treatment including 0.9% isotonic infusion (1 mL/kg/h, upper limit 100 mL/h) and N-acetylcysteine 600 mg twice daily as our previous study (11). The usage of N-acetylcysteine with fluid infusion was recommended in guideline as a class II recommendation but only N-acetylcysteine administration was not recommended (12).

Statistical analysis

The SPSS statistical software (SPSS for Windows15.0, Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean±standard deviation (SD), and categorical variables were defined as percentage. Continuous variables were analyzed with Kolmogorov-Smirnov for testing normal distribution. Differences between groups were tested using one-way analysis of variance (ANOVA), Mann-Whitney U, Kruskal-Wallis and Chi-square test when appropriate. Paired t-test and Wilcoxon signed ranks test were used to compare differences within groups following an intervention. We performed binary logistic regression with the presence of CIN as the dependent variable and the following as potential covariates: age, eGFR, contrast amount, serum creatinine, left ventricular ejection fraction, Mehran score, presence of hypertension, diabetes mellitus, RAAS blocker use, female gender, hyperlipidemia and history of coronary artery disease. Variables that were statistically significant in univariate analysis were included in the final multivariate model to identify predictors of CIN. A two-sided 95% confidence interval (CI) was constructed around the point estimate of the odds ratio (OR). All tests were two-sided, and a p value of less than 0.05 was considered for statistical significance.

Statistical power of this study was calculated for CIN, it was found as 98.6%.

Results

Demographic and baseline characteristics

Baseline characteristics were comparable for 3 groups except hypertension. Prevalence of hypertension was significantly higher (p<0.05) in RAAS blocker group (ACEI and ARB) than no RAAS blocker group as expected. Contrast agent's type and volume were comparable for 3 groups (Table 1).

Primary and secondary end-point outcome

When we compared ARB and no RAAS blocker group, CIN was significantly higher in ARB than no RAAS blocker group [17 (18.1%) vs. 7 (7.4%) respectively, p=0.04]. Although CIN was higher in ACEI than no RAAS blocker group, p value did not reach significance [18 (17.0%) vs. 7 (7.4%) respectively, p=0.06]. CIN rate was significantly higher in ACEI and ARB (RAAS blocker group) than no RAAS blocker group [35 (17.5%) vs. 7 (7.4%) respectively, p=0.01] (Fig. 1). Our secondary end-point delta Cre was comparable for ACEI, ARB and no RAAS blocker groups (0.08±0.2, 0.12±0.3 and 0.09±0.3 mg/dL, respectively, p=0.25).

When the subgroup of patients with eGFR 30-60 mL/min was analyzed, there was no statistical significant difference for CIN between ACEI, ARB and no RAAS blocker groups (30.8%, 25.0% and 11.5%, respectively, p=0.23).

Table 1. Baseline characteristics of study patients

Variables	All groups (n=295)	No RAAS (n=95)	ACEI (n=106)	ARB (n=94)	*p
Age, years	63.8±12.7	61.9±12.9	64.1±12.0	65.4±13.1	0.16
Female, %	28.5	28.4	23.6	34.0	0.26
Hypertension, %	60.7	27.4	75.5	77.7	<0.001
SBP, mmHg	126.7±14.5	124.4±11.0	127.7±14.6	128.0±17.2	0.21
DBP, mmHg	78.2±10.9	76.4±9.5	79.2±10.5	78.9±12.6	0.10
Diabetes mellitus	34.6	33.7	34.0	36.2	0.92
Hyperlipidemia	52.5	54.7	50.9	52.1	0.86
History of CAD	23.7	17.9	23.6	29.8	0.40
eGFR (baseline), mL/min	87.0±35.1	87.9±34.6	89.3±37.1	83.5±33.3	0.49
Creatinine, mg/dL	0.98±0.31	1.00±0.32	0.97±0.33	0.97±0.26	0.77
LVEF, %	47.9±12.8	46.9±13.7	48.5±12.5	48.4±12.3	0.73
Contrast volume, mL	111.0±34.4	110.0±25.8	111.7±38.6	111.1±37.1	0.37
Iodixanol, %	21.4	18.9	23.6	21.3	0.53
Ioxaglate, %	40.7	46.3	40.6	35.1	0.53
Iopromide, %	38.0	34.7	35.8	43.6	0.53
Mehran score	4.64±3.78	4.51±3.72	4.55±3.86	4.86±3.78	0.81
Preventive treatment, %	20.3	21.1	16.0	24.5	0.32
Patients with (30 ≤eGFR baseline <60), n (%)	76 (25.8)	26 (27.4)	26 (24.5)	24 (25.5)	0.89

Continuous variables are presented as mean±SD, and categorical variables are presented as percentage
*ANOVA. Kruskal-Wallis and Chi-square tests
ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker, CAD - coronary artery disease, DBP - diastolic blood pressure, eGFR - estimated glomerular filtration rate, LVEF - left ventricular ejection fraction, RAAS - renin angiotensin aldosterone system, SBP - systolic blood pressure.

CIN predictors

When the patients with and without CIN were compared, percentage of hypertension, Mehran score, age and baseline serum creatinine were significantly higher, baseline eGFR was significantly lower in patients with CIN (Table 2). When we per-

form multivariate analysis, we found Mehran score and RAAS blocker usage as independent predictors for CIN (Table 3).

All study population analyzed for serum creatinine and eGFR. After contrast administration, serum creatinine significantly increased (0.98±0.31 vs. 1.08±0.47 mg/dL, p<0.05) and eGFR significantly decreased (87.0±35.1 vs. 82.4±36.0 mL/min, p<0.05).

Discussion

The main finding of our study was significantly higher incidence of CIN in chronic RAAS blocker users compared to patients with no RAAS blocker treatment. In the baseline characteristics, only hypertension was significantly higher in our RAAS blocker group. It is actually associated with our selection bias. This factor could indeed affect the primary endpoint of CIN development, as hypertension is a well-known risk factor for nephrosclerosis. However, considering the similar baseline values of eGFR, systolic and diastolic blood pressures in 3 subgroups, we thought that the effect of hypertension on CIN could be ignored. Multivariate analysis also confirmed this assumption, presenting chronic RAAS blocker usage as an independent predictor of CIN development. The second main finding was Mehran score which was the only other independent predictor of CIN even in our low-risk study population. Mehran risk score is an important parameter which can predict the risk of CIN in patients with elective coronary procedures and also with acute coronary syndromes. Recently it has been shown that Mehran risk score was also successful in predicting long-term major adverse cardiac event and mortality in acute myocardial infarction patients treated with percutaneous coronary intervention (13).

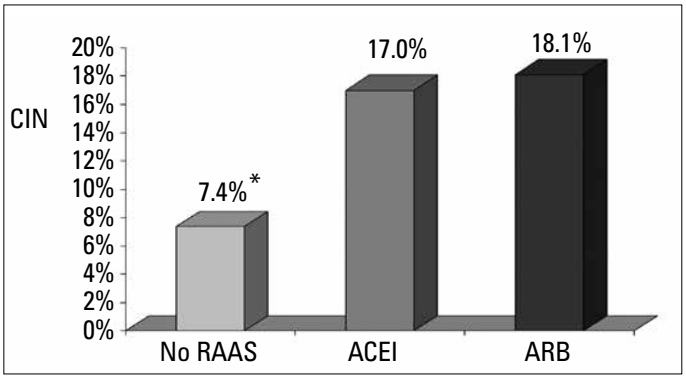

Figure 1. Comparison of CIN percentage between groups
Chi-square test
*p=0.04 for No RAAS and ARB groups, p=0.02 for No RAAS and RAAS (ACEI+ARB) groups, p=0.06 for No RAAS and ACEI groups

Table 2. Clinical variables in patients with and without CIN

Variables	CIN (+) (n=42)	CIN (-) (n=253)	*p
Age, years	68.8±10.0	63.0±12.9	0.006
Hypertension, %	76.2	58.1	<0.001
Mehran score	7.0 (0-16)	4.0 (0-14)	<0.001
eGFR (baseline), mL/min	70.1±27.2	89.8±35.5	0.001
Creatinine (baseline), mg/dL	0.9 (0.5-2.38)	1.0 (0.57-2.30)	0.013

Variables are presented as mean±SD and as percentage
*t-test for independent samples, Mann-Whitney U test and Chi-square test
CIN - contrast-induced nephropathy, eGFR - estimated glomerular filtration rate

Table 3. Independent predictors of CIN according to binary logistic regression analyses

Variables	Odds Ratio	95% CI	p
Age	0.993	0.947-1.042	0.78
eGFR (baseline)	0.994	0.974-1.015	0.58
Cre (baseline)	1.433	0.344-5.966	0.62
Hypertension	0.898	0.373-2.164	0.81
Mehran score	1.15	1.019-1.310	0.02
RAAS blocker	2.69	1.025-7.067	0.04

Cre - creatinine, CI - confidence interval, eGFR - estimated glomerular filtration rate, RAAS - renin angiotensin aldosterone system

In our study, mean creatinine of all study population was 0.98±0.31 (0.50-2.38) mg/dL which indicates a relatively good baseline kidney function compared to the other similar studies in literature. The mean eGFR of the total study population was 87.0±35.1 mL/min and the percentage of the patients whose eGFR below 60 was only 25.8%. Average Mehran score of our group was also relatively low. These findings were related to our inclusion criteria as we had excluded the patients with unstable clinical conditions. As a result, we can say that, our study group consisted of low risk, stable patients with nearly normal renal functions who underwent elective intervention. In daily clinical practice, vast majority of patients who underwent coronary angiography are similar to our study population. As mentioned previously, reports regarding the effects of RAAS blockers on CIN development are mostly focused on patients with mild to moderate renal impairment. At this point this study is the first showing the effects of chronic RAAS blocker usage on CIN development in patients with normal renal functions.

Controversial results for relation of ACEI, ARB and CIN were reported in literature. Some studies reported RAAS blockers were preventive for CIN (6, 7). A study by Gupta et al. (7) in India randomized patients to captopril 25 mg TID for three days (starting 1 h prior to contrast administration) and found a 79 % risk reduction in developing CIN compared to controls who received no therapy. It has been speculated that ACEIs may confer protection against CIN by counteracting afferent arteriolar vasoconstriction and subsequent medullary ischemia caused by angiotensin II activation after contrast administration. On the contrary, the vast majority of the studies reported that RAAS blocker cause deterioration of renal functions. In a recent study Hölscher et al. (14) prospectively assess predictors of CIN and long-term outcomes of affected patients. Utilizing the data from the 412 patients studied in the Dialysis-Versus-Diuresis (DVD) trial, post-procedural hemodialysis, left ventricular ejection fraction <35%, serum phosphate, and ACEI use were found to be independently associated with increased incidence of CIN. ACEI

intake was associated with a six-fold increase in the incidence of CIN post-procedure (OR 6.16, 95% CI 2.01-18.93) (14). ACE inhibitors prevent the conversion of angiotensin I-II, thus releasing the vasoconstriction of the efferent glomerular arterioles, with a subsequent decrease in the glomerular hydrostatic pressure. With a lower glomerular hydrostatic pressure, there is less glomerular filtration (15). It has been suggested that this decrease in eGFR may predispose to the development of CIN in patients taking ACEI and ARB (4, 5). Most of the studies investigated the effect of continuation or acute withdrawing of RAAS blockers. Rosenstock et al. (16) investigated the patients with chronic kidney disease (Stage 3-4) who are on chronic ACEI-ARB therapy (16). They continued or discontinued the drug 24 h before coronary angiography. Additionally, they had a no RAAS blocker group. The authors found no statistically significant differences between the groups in the incidence of CIN: continuation group 6.2%, discontinuation group 3.7%, and no RAAS blocker group 6.3% (p=.66). Rosenstock et al. (16) concluded that ACEIs do not increase the incidence of CIN. They recommended not withholding ACEIs prior to contrast exposure. However a recent report from Mayo clinic suggests withdrawal of RAAS blocker usage 24-48 hour before elective interventions, relying on their own clinical experience and also an earlier literature data (17, 18). Chronic ACEI administration was investigated by Cirit et al. (5). They found that chronic ACEI administration was a risk indicator of CIN. CIN occurred in 17 patients in the ACEI group and 7 patients in the control group (15.6% vs. 5.8%, p=0.015). In this study, the study population was also consisted of patients with mild to moderate renal insufficiency. Recently a review has been published by Patel et al. (19). This review focused on the role of ACEIs in CIN. In this review, the results of 5 randomized clinical trials and 678 patient were analyzed. Based on these data they concluded that there is no definite correlation between ACEIs and the occurrence of CIN in the cardiac catheterization laboratory and withholding ACEIs prior to catheterization does not probably decrease the incidence of CIN and is not recommended. They also stated that starting ACEIs before the procedure for the sole purpose of lowering the risk of CIN cannot be recommended based on the current evidence (19).

The presence of different conclusions can result from significant differences in methodology, study populations, interventions. The possible consideration of potential factors contributing to ACE inhibitors in prevention of contrast-induced nephropathy included baseline Cre levels, volume of contrast media, age, diabetes mellitus, dose, and the structure of ACEIs. Besides, the definition of contrast-induced nephropathy was also variable among the studies.

Renin-angiotensin-aldosterone system blockers constitute a major treatment modality for cardiovascular and renal diseases, and the use of ACEIs is very common among patients undergoing coronary angiography. Currently, it is not known whether withholding ACEIs before angiography is a potential preventive measure for CIN. However chronic usage of RAAS blockers seems to be a risk factor for CIN development. Previously this was proven in patients with mild to moderate renal insufficiency. In this study, it is shown that chronic RAAS blocker usage is also a risk factor for CIN development in patients with near normal renal functions. This study is also the important in regard of results related to ARB. Angiotensin receptor blockers were found to increase the CIN development significantly. This association was even stronger in ARB group compared to ACEI group. In a recent study, impact of ACEI and ARB on the frequency of CIN was evaluated through a post hoc analysis from the DVD trial (20). This study showed that patients receiving ACEI or ARB while undergoing cardiac catheterization significantly more often developed CIN within 72 h after coronary procedure. However, in this study, patients receiving ACEI or ARB were not evaluated separately. Moreover only 12% of the patients with RAAS treatment, were ARB users, that the impact of ARB on CIN development was not analyzed in a separate manner.

Study limitations

Our study has some limitations. First of all, it has a single-center design that the results could better be generalized if they will be repeated in other future trials. Second, the dose and the structure of the ACEI and ARB were not homogeneous among the groups. Although we had data about the structure of the drugs, we did not further analyze as the patient numbers in subgroups would be too small for interpreting the data.

Conclusion

The results of the present study show that in patients with near normal renal functions who are undergoing elective coronary procedure, chronic use of ACEI and ARB increase the risk of CIN. In daily practice, considering this finding could be particularly important in the pre-procedural risk assessment of the patients.

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