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Original Article

Evaluation of renoprotective effect of calcium channel blockers in coronary angiography patients

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ABSTRACT

Aim: To evaluate the effectiveness of contrast-induced acute kidney injury (CI-AKI) prophylaxis retrospectively, using calcium channel blockers (CCB) before and after contrast exposure and comparing them with patients using angiotensin converting enzyme inhibitors (ACEI), which has not been explored by many studies.

Methods: The study was performed in Afyon Kocatepe University, Faculty of Medicine Research Hospital, Cardiology Department between January 2014 and June 2016. Eighty patients using dihydropyridine (amlodipine 10 mg), non-dihydropyridine (diltiazem 60 mg) CCB or ACEI in the form of monotherapy before coronary angiography were included.

Results: In the CCB and ACEI group, CI-AKI development rates were 15.7% (n=8) and 24.1% (n=7), respectively *(p = 0.383; Fisher's exact test)*. When the CCB group was evaluated as dihydropyridine and non-dihydropyridine subsets, CI-AKI development rates were found to be similar as well *(p = 0.445; Fisher's exact test)* in each subset.

Conclusion: In our study, we evaluated one of today's important dilemma; the methods related to the prophylaxis of CI-AKI. Our study shows that there is no difference in the development of CI-AKI between patients using the calcium channel blocker group drugs and ACEI as monotherapy. However, in our study, the mean age of patients using CCB was significantly higher than the group using ACEI.

Keywords: Contrast-induced acute kidney injury, calcium channel blockers, angiotensin converting enzyme inhibitors, renoprotective effect.

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Introduction

Contrast media (CM) has a plethora of applications in routine non-invasive or percutaneous invasive imaging examinations and therapeutic interventions. Unfortunately, the use of CM is associated with a number of complications, the most serious being contrast-induced acute kidney injury (CI-AKI) [1].

A general definition of CI-AKI is an impairment in renal function occurring within 3 days following the intravascular administration of CM and the absence of an alternative etiology [2]. Contrast media administration has been said to be the third leading cause of

hospital-acquired acute renal failure in the past 3 decades [3]. Chronic kidney disease, dehydration, diabetes mellitus (DM), advanced age, increased volume of CM and recurrent administrations are well-known risk factors of CI-AKI [4].

In spite of the vast clinical importance of CI-AKI, its understanding and the pathophysiology behind CI-AKI is not fully explained [2, 3]. Most reviews show a complex pathophysiology overlaying medullary ischemia and hypoxia, oxidant damage, intratubular obstruction, hypertonicity, plasma viscosity and many pathways including endothelins, nitric oxide, reactive oxygen species, prostaglandins and adenosine [5].

Calcium has been proposed as a mediator of the vasoconstrictor response to CM [6]. Also Intracellular Ca^{2+} overload is considered to be a key factor in CI-AKI [3]. The rationale is based on the fact that while in normal subjects, the Na^+-Ca^{2+} exchanger pumps Ca^{2+} outside the renal tubular epithelial cells to keep intracellular Ca^{2+} low. Under the effect of CM, the Na^+-Ca^{2+} exchanger can reversibly extrude Na^+ for Ca^{2+} influx, thereby leading to intracellular Ca^{2+} overload, which is considered a key factor in ischemic cell injury and in CI-AKI [7]. The increase in intracellular calcium provokes a vasoconstrictive response in intrarenal circulation and would been important mediator of epithelial cell apoptosis and necrosis. Thus, calcium channel blockers (CCB) have been hypothesized to have protective effects against CI-AKI [8]. The CCB attenuated the vasoconstrictor response of CM in animal studies, although prophylactic use of CCB has not gained wide acceptance [6]. Literature show opposing results; some authors suggesting them to be protective [9, 10], others finding no benefit at all [11-13]. However, these researches are very old and more recent studies are needed. In this study we compared patients who used dihydropyridine (amlodipine 10 mg), nondihydropyridine (diltiazem 60 mg) CCB and ACEI; and underwent coronary angiography. We compared serum creatinine, blood urea nitrogen (BUN), urea levels and glomerular filtration rates (GFR) before and 3-15 days after the coronary angiography. We planned to examine the changes in the GFR values by taking demographic data into consideration.

Materials and methods

We used a definition of CI-AKI which is widely accepted; impairment in renal function occurring within 3 days following the intravascular administration of CM and the absence of an alternative etiology [2].

The study included 80 patients using dihydropyridine, non-dihydropyridine CCB and ACEI from 4027 patients who underwent coronary angiography in the Cardiology department of Afyon Kocatepe University, Faculty of Medicine, Research Hospital between January 2014 and June 2016. Information about patients was obtained by retrospectively examining patient files. Prior to the study, the necessary ethics committee approval was obtained (Decision no; 29-5-2016). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Inclusion and exclusion criteria: Of the 4027 patients; only 80 patients used dihydropyridine (amlodipine 10mg), nondihydropyridine (diltiazem 60mg) or ACEI before coronary angiography as monotherapy. 2635 patients using multidrug therapies were excluded. Also

1074 patients were excluded because they were not using CCB or ACEI.

Individuals under the age of 18 and over 85 were not included in the study (total of 84 patients). Data was obtained by retrospectively scanning patient files. Patients were included in the study if the registration data were sufficient. Patients were excluded if serum creatinine, BUN, urea levels and GFR value within 3 to 15 days of coronary angiography were not in the database. Also patients with missing demographic data were excluded. 154 patients were excluded because of a missing data in their files.

Statistical Analysis

The data of the patients' who are included in the study has been collected and submitted in a database for the study. These variables include; age, gender, smoking habits, body mass index (BMI), hypertension duration (in years), systolic and diastolic blood pressure measurements, comorbid disease, patients laboratory findings (before and after contrast exposure) including hemogram, BUN, serum creatinine, urea, glomerular filtration rate (GFR), lipid analysis, and electrolytes. Data was analyzed using IBM SPSS 18.0. Descriptive statistical results of the study data were expressed as arithmetic mean ± standard deviation. While evaluating the groups, patient distributions were given as frequencies. The data obtained were evaluated primarily with descriptive statistics. The suitability of the data to the parametric conditions was evaluated with the Kolmogorov-Smirnov test. Mann-Whitney U test was used for the quantitative evaluation between the CCB and ACEI groups. Wilcoxon Test was used to compare the median values of the two dependent groups, and the Chi Square test was used to compare the categorical data and the groups. In the results obtained from the

statistical tests applied, it was considered significant when a 95% confidence interval (CI) and the *p-value below 0.05.*

Results

When the demographic data of the patients included in the study were evaluated, 55 (68.8%) were male and 25 (31.2%) were female. There were 29 (56%) men, 22 (44%) women in the patient group using calcium channel blocker; and 26 (89%) men and 3 (11%) women in the ACEI group. There was a significant difference in gender distribution between the two groups *(p = 0.002).* The mean age of the patients was 60.4 ± 12.5. When analyzed as CCB and ACEI groups, the average age of patients using CCB was 62.6 ± 12.6, and the average age of the patient group using ACEI was 56.5 ± 11.5. The mean ages of the two groups were found to be statistically different *(p = 0.01).* BMI was similar between the CCB group and the ACEI group *(p = 0.222).* When systolic blood pressures of patients were evaluated, mean systolic blood pressure was 132.9 ± 15.3 (range: 110-180) mmHg in the CCB group and 119.1 ± 10.6 (range: 86-140) mmHg in the group using ACEI. Systolic blood pressure was significantly higher in the CCB group than the ACEI group *(p <0.001).* Again, when groups using CCB and ACEI were compared, diastolic blood pressures were similar *(p = 0.663).* The duration of involved drug use in both groups was similar *(p <0.233).* Of the 80 patients who are enrolled in the study, 25 had no other comorbid disease. 31 (38, 8%) had DM, 5 (6.3%) had a history of cerebrovascular disease, 7 (8.8%) had congestive heart failure, 3 (3.8%) had peripheral arterial disease, 15 (18.8%) had hyperlipidemia, 10 (12.5%) had chronic lung disease. Disease distributions were similar in CCB and ACEI groups *(p> 0.5).*

When the drugs used by patients were classified, 21 people were using nondihydropyridine (diltiazem 60mg), 30 people were using dihydropyridine (amlodipine 10 mg) and 29 people were using ACEI.

When staged according to the JNC8 report, only 10 of the 80 patients were found to have optimal systolic and diastolic blood pressure. Despite the use of CCB, blood pressure levels of 5 patients were found to be stage-2 hypertension. It was found that patients using trandolapril had more effective control over blood pressure compared to patients using CCB.

The laboratory values of the two groups are presented in Table 1. When the laboratory values of the two groups were compared, the hemoglobin, hematocrit, platelet, fasting blood glucose, uric acid, calcium (Ca), AST, ALT, lipid panel (LDL, VLDL, HDL, total cholesterol, triglyceride) values were also similar between the CCB group and the ACEI group. There was a significant difference between phosphorus and HbA1c levels between the two groups. Serum phosphorus level in the CCB group was 2.6-4.5 (mean 3.51 ± 0.5) mg / dl, and in the group using ACEI 1.5-4.2 (mean 3.1 ± 0.6) mg/dl *(p = 0.043)*. The HbA1c level

Table 1. Comparison of laboratory parameters of two groups.

Laboratory Parameters	CCB Group		ACEI Group		*p-value*
	Min-max	**Mean**	**Min-max**	**Mean**	
Hb(g/dl)	9- 17	12.7±2.0	9,6-17,0	13.07±2.1	*0.538*
Htc (%)	28-57	40.3±6.5	29-50	40.6±6.1	*0.641*
Plt (x10³)	66-369	232.3±64.3	177-352	239.4±55	*0.944*
FBG (mg/dl)	60-377	142.6±65,9	74-358	158.5±76.5	*0.597*
Uric Acid (mg/dl)	2,8-27	5.8±3.5	2.8-12	5.6±2	*0.768*
Ca^{++} (mg/dl)	7,9-10	9.1±8.7	7,8-10	9.1±0.5	*0.864*
Phosphorus (mg/dl)	2,6-4,5	3.51±0.5	1,5-4,2	3.1±0.6	***0.043***
K$^+$ (mEq/l)	3,1-5,5	4.4±0.5	3,2-5,1	4.4±0.4	***0.028***
HbA1c %	5,3-12	7.8±1.8	9,0-13,0	10.4±1.6	***0.017***
AST (U/L)	13-78	26.7±12.5	12-206	40.4±38.7	*0.222*
ALT (U/L)	5-167	28.8±31.4	8-61	22.8±12.08	*0.980*
LDL (mg/dl)	25-228	114.2±46.3	51-212	108.5±40.9	*0.572*
VLDL (mg/dl)	9-106	31.8±17.5	9-63	29.2±14.2	*0.663*
HDL (mg/dl)	14-68	37.7±12.4	16-61	36.4±10.1	*0.676*
Total cholesterol(mg/dl)	120-324	168.1±58.8	84-284	161.1±48.6	*0.420*
Triglyceride(mg/dl)	85-531	151.4±94.0	48-316	147.5±72.3	*0.890*

CCB: calcium channel blockers, ACEI: angiotensin converting enzyme inhibitors Hb: Hemoglobin, Htc: hematocrit, Plt: Platelet, FBG: fasting blood glucose.

was 5.3-12% (mean: 7.8 ± 1.8) in the CCB group and 9-13% (10.4 ± 1.6) in the group using ACEI *(p = 0.017)*. Serum potassium level was 4.2 ± 0.5 mEq/dl in the CCB group, and 4.4 ± 0.4 mEq/dl in the ACEI group. There was a significant difference between the potassium levels of two groups *(p = 0.02)*.

Pre-contrast exposure serum creatinine, BUN, urea and GFR were similar *(p values = 0.359, 0.904, 0.707, 0.426, respectively)*. The mean urea of the group using CCB after contrast exposure was 43.1 ± 23.0 mg/dl, and 38.9 ± 23.6 mg/dl in the ACEI group *(p = 0.08)*. Cr value of CCB group was 1.06 ± 1.4 mg/dl, and 1.0 ± 0.4 mg/dl in the ACEI group *(p = 0.11)*. After contrast exposure, GFR was calculated as 85.9±27.9 (ml/min/1.73m2) for the CCB group and 88.9±33.9 (ml/min/1.73m2) for the ACEI group. When the two groups were compared in terms of GFR levels after contrast exposure, they were found similar *(p = 0.818)*.

In the CCB and ACEI groups, CI-AKI development rates were 15.7% (n=8) and 24.1% (n= 7), respectively. The two groups were similar in terms of CI-AKI development rates *(p = 0.383; Fisher's exact test)*.

When the CCB group was evaluated as dihydropyridine and nondihydropyridine groups, the rates of CI-AKI were similar *(p = 0.445; Fisher's exact test)*.

Discussion

CI-AKI has become an important problem as a result of the increased use of contrast today. Again, it increases the life-threatening complications such as sepsis, bleeding, and respiratory failure, and increases the hospital stay and leads to an increase in medical costs. Prevention and treatment of such an important complication is very essential for the physician, patient and the country's economy. The data obtained up to this day confirms the idea that

the volume expansion method is the most important method for reducing the risk of CI-AKI [14]. But the pathophysiology behind CI-AKI is not fully explained [2, 3]. Therefore search for a prophylaxis of CI-AKI still continues.

Intracellular Ca^{2+} overload is an important factor in ischemic cell injury and considered to be a key factor in CI-AKI pathophysiology [3]. Therefore CCB, which could prevent intracellular Ca^{2+} overload, have been suggested as a protective measure to prevent CI-AKI [7]. However previous data shows conflicting results. Most of the animal studies on rats showed promising results. Yu-Yan Fan et al., Aritomi et al. and Duan et al. all showed similar renoprotective effects of CCB [15-17]. Beyazal et al. [14] compared isotonic sodium chloride infusion alone, 5% dextrose solution with sodium bicarbonate infusion and isotonic sodium chloride infusion plus 3 days of CCB therapy (one day before and two days after the contrast exposure) for CI-AKI prophylaxis. They find no significant difference between groups.

Arici et al. [18] also find no significant difference in a prospective study with patients pretreated with amlodipine; a dihydropyridine CCB; than placebo. Whereas Russo et al. [10] reported that CCB nifedipine may prevent AKI induced by hyperosmolar contrast agent. Neumayer et al. [9] investigated a total of 35 patients after intravascular administration of contrast media to determine the effects on renal function of a 3-day treatment with the CCB nitrendipine (n=16), compared the findings in a placebo-treated control group (n=19). Prophylactic use of nitrendipine preserved the glomerular filtration rate, whereas control patients showed a significant (27%) reduction in GFR two days after contrast-media injection *(p≤0.01)*. As a result, it was emphasized that

nitrendipine, a nondihydropyridine CCB, could decrease the risk of CI-AKI [9].

In our study we compared two groups, who were using ACEI and CCB as monotherapy; and found no significant difference in development of CI-AKI. But this can be an effect of ACEI as well as CCB. ACEI also have been used to prevent CI-AKI in the past. Gupta et al. conducted a study of 71 patients who underwent coronary angiography and concluded that ACEI is effective against CI-AKI compared to placebo [19]. But more recent studies find no beneficial effect of ACEI. Furthermore Toprak et al. reported that in a randomized controlled study of 80 patients included; five patients (8.3%) in the ACEI group and 1 patient (3%) in control group developed CI-AKI and this difference was statistically significant *(p=0.02)*. They concluded that using ACEI is a risk factor for development of CI-AKI [20]. In our study, 8 (15.7%) patients in CCB group and 7 (24.1%) patients in ACEI group developed CI-AKI. The two groups were similar in terms of CI-AKI development rates statistically *(p = 0.383)*. This may be the result of both drugs lowering the risk factor of CI-AKI equally.

Age is a direct risk factor of developing CI-AKI. Especially elderly patients older than 70-75 years are at risk of developing CI-AKI [7]. Hui et al. showed in their study that amlodipine, a CCB, may decrease the risk of developing CMN in elderly patients [21]. In our study, the mean age of the CCB group was significantly higher than the ACEI group. The mean age of the patients in CCB group was 62.6 ± 12.6, against the mean age of the patients in ACEI group was 56.5 ± 11.5 *(p = 0.01)*. This could mean that CCB reduced the risk of older patients in the CCB group to a younger age risk level. Therefore two groups statistically appear indifferent in CI-AKI development rates.

Oguzhan et al. compared hydration therapy alone, versus valsartan-amlodipine combination plus hydration treatment in patients who have stage-II chronic kidney disease and going through coronary angiography. CI-AKI rates was 17.8% (n=8) in the CCB/ARB plus hydration group and 6.7% (n=3) in the only hydration group. As a result, they showed that amlodipine and valsartan treatment did not decrease the risk of CI-AKI [22]. Davidson et al. prospectively examined 1144 patients undergoing cardiac catheterization. They showed that the risk of developing CI-AKI does not decrease in patients using various CCB drugs [23]. In their prospective randomized study, Arıcı et al. [18] divided the 29 patients into two groups of amlodipine (n=15) and placebo (n= 14). Only one patient developed CI-AKI in each group. Two groups were similar statistically regarding CI-AKI development rates (amlodipine group: 6.6% n=1; placebo group: 7.1% n=1). Although our study was designed retrospectively, it is important to show similar results and rates with these three prospective studies.

The main limitations of our study are retrospective study design and relatively small sample size. Also; age difference between two groups and the fact that we could not randomize groups for contrast dose and their hydration status is a limitation of our study.

Conclusion

In our study, we evaluated one of today's important dilemma; the methods related to the prophylaxis of CI-AKI. Our study shows that there is no difference in the development of CI-AKI between patients using the CCB and ACEI as monotherapy. However, in our study, the mean age of patients using CCB was significantly higher than the group using ACEI. The volume expansion method is the most

favorable method for reducing the risk of CI-AKI and the pathophysiology behind CI-AKI is not fully explained. Therefore we need more studies exploring CI-AKI prophylaxis.

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *The study was reviewed and approved by the local ethics committee (Decision no; 29-5-2016)*

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