

Effect of renin-angiotensin-system blockers on contrast-medium-induced acute kidney injury after coronary angiography

Ja-Jun Goo¹, Jae-Joon Kim¹, Ji-Hoon Kang¹, Kyoung-Nyoun Kim¹, Ki-Sup Byun¹, Mi-kyung Kim², and Tae-Ik Kim¹

¹Department of Internal Medicine, Maryknoll Medical Center, Busan; ²Department of Internal Medicine, Inje University College of Medicine, Busan, Korea

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Correspondence to
Tae-Ik Kim, M.D.

Division of Cardiology, Department of Internal Medicine, Maryknoll Medical Center, 121 Junggu-ro, Jung-gu, Busan 600-730, Korea
Tel: +82-51-461-2429
Fax: +82-51-465-7470
E-mail: kimti2429@gmail.com

Background/Aims: With the increasing incidence of cardiovascular disease, angiocardiology using contrast-enhancing media has become an essential diagnostic and therapeutic tool, despite the risk of contrast-medium-induced acute kidney injury (CIAKI). CIAKI may be exacerbated by renin-angiotensin-system (RAS) blockers, which are also used in a variety of cardiovascular disorders. This study evaluated the effects of RAS blockade on CIAKI after coronary angiography.

Methods: Patients who underwent coronary angiography in our hospital between May 2009 and July 2011 were reviewed. Serum creatinine levels before and after coronary angiography were recorded. CIAKI was diagnosed according to an increase in serum creatinine > 0.5 mg/dL or 25% above baseline.

Results: A total of 1,472 subjects were included in this study. Patients taking RAS blockers were older, had a higher baseline creatinine level, lower estimated glomerular filtration rate (eGFR), and had received a greater volume of contrast medium. After propensity score matching, no difference was observed between the RAS (+) and RAS (-) groups. Multiple logistic regression identified RAS blockade, age, severe heart failure, contrast volume used, hemoglobin level, and eGFR as predictors of CIAKI. Multiple logistic regression after propensity matching showed that RAS blockade was associated with CIAKI (odds ratio, 1.552; $p = 0.026$).

Conclusions: This study showed that the incidence of CIAKI was increased in patients treated with RAS blockers.

Keywords: Renin angiotensin system; Coronary angiography; Acute kidney injury

INTRODUCTION

Recent advancements in angiocardiology have contributed to the rapid diagnosis and treatment of ischemic heart disease. The use of contrast-enhancing media, in particular, has become essential in this and other imaging modalities, resulting in a rapid increase in their use [1]. However, the use of contrast media has been linked to a nonoliguric form of acute kidney injury, known as contrast-medium-induced

acute kidney injury (CIAKI), that is characterized by an increase in serum creatinine levels within 48 to 72 hours of exposure to contrast medium [1-6]. CIAKI is the third most common cause of acute renal failure among in-patients [2,7,8]. Elevated serum creatinine levels typically normalize within 7 to 10 days, although in some cases the condition may progress to chronic renal disease [1,5].

The pathophysiological mechanism of CIAKI has not been elucidated. One of the most important risk

factors for CIAKI is existing chronic renal disease [2,9,10]; however, age, the volume of contrast medium used, concurrent diabetes mellitus (DM), congestive heart failure, and anemia have also been implicated. CIAKI is primarily classified as an acute ischemic kidney injury caused by vasoconstriction due to contrast agents, but other potentially contributing mechanisms include direct tubular toxicity as well as impaired vasodilation of renal vessels due to increased endothelin and reduced nitric oxide levels [11].

In addition to contrast media, the use of renin-angiotensin-system (RAS) blockers is increasing in a variety of cardiovascular disorders. RAS blockers, such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), are used to control hypertension and subsequent complications in at-risk patients. However, conflicting results regarding the impacts of RAS blockade on CIAKI have been reported. Some studies have shown that long-term use of RAS blockade is a risk factor for CIAKI and should be halted before performing contrast studies [2,12], whereas others have reported that RAS blockade protects against CIAKI [13]. To gain insight into these conflicting views, we retrospectively reviewed the medical records of patients who underwent contrast coronary angiography with or without RAS blockade, and we evaluated the impacts of ACEI and ARB use on the incidence of CIAKI.

METHODS

Study design and objectives

The impacts of RAS blockade on CIAKI were evaluated by conducting a retrospective observational study with patients who successfully underwent coronary angiography in our hospital between May 2009 and July 2011. Indications for angiocardiology included suspected or known cardiovascular disease, congestive heart failure, and cardiac valve diseases. Only patients with creatinine levels < 2.0 mg/L were included in this study to minimize the confounding effect of chronic kidney disease on CIAKI incidence. Patients were excluded if they showed creatinine levels > 2.0 mg/L, if they required dialysis, if they did not require contrast medium, if pretreatment or posttreatment creatinine

data were lacking, or if they required further contrast studies.

CIAKI was diagnosed if serum creatinine levels increased > 0.5 mg/dL or > 25% of baseline within 48 to 72 hours after angiocardiology. Baseline creatinine levels were determined before angiocardiology or any other contrast study. The same contrast medium was used for all subjects. The Cockcroft-Gault equation was used to calculate the estimated glomerular filtration rate (eGFR), as follows:

$$\text{eGFR (mL/min)} = \frac{[(140 - \text{age}) \times \text{mass} \times 0.85 \text{ if female}]}{(72 \times \text{serum creatinine})}$$

Severe congestive heart failure (HF) was defined as having an ejection fraction (EF) \leq 35%. Subjects were also analyzed with respect to smoking status.

Statistical analyses

Data were analyzed using *t* tests, chi-square tests, and multiple logistic regression using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Covariates used in the multiple logistic regression analysis were age, contrast medium volume, eGFR, hemoglobin level, presence of DM, gender, smoking, and severe congestive HF.

To account for covariates that may have influenced whether or not a patient received a given treatment, propensity score matching was performed using the SAS version 9.1 (SAS Institute Inc., Cary, NC, USA), and patients without a corresponding match were excluded. Propensity scores were calculated by modeling the probability of receiving an RAS blockade agent. The probability was predicted by multiple logistic regression, for which the *p* was 0.087 and C-statistic was 0.646 using the Hosmer-Lemeshow goodness-of-fit test. Regression analysis was then repeated for these matched subjects.

RESULTS

A total of 2,047 patients who underwent coronary angiography were reviewed. Of these, 1,472 patients who met the inclusion criteria were enrolled. The subjects were divided into patients who received RAS blockade (RAS blockade [+]) and patients who did not (RAS blockade

(-)) (Table 1). The percentage of patients receiving RAS blockade was 28% in our study group. The mean age (\pm standard deviation) was 61.39 ± 11.40 years in the RAAS blockade (-) group and 64.56 ± 10.14 years in the RAAS blockade (+) group ($p < 0.001$). Contrast dye volume was significantly higher in RAAS blockade (+) group than RAAS blockade (-) group (209.54 ± 106.39 mL vs. 184.17 ± 104.79 mL). No significant difference was observed in number of patients with severe heart failure ($EF \leq 35\%$) between groups. Compared to the RAAS blockade (-) group, the RAAS blockade (+) group had a significantly lower mean hemoglobin level, mean eGFR, the percentage of male, the percentage of current smoker and the percentage of DM (Table 1). In unmatched subjects, RAS blockade was not a significant risk factor for CIA-

KI in the univariate regression, but became significant in the adjusted multiple regression analysis (adjusted odds ratio [OR], 1.372; $p = 0.048$) (Table 2). Other significant predictors for CIAKI were age (adjusted OR, 1.027; $p = 0.007$), severe HF (adjusted OR, 12.454; $p < 0.001$), contrast or dye volume used (adjusted OR, 0.997; $p = 0.001$), hemoglobin level (adjusted OR, 0.899; $p = 0.031$), and eGFR (adjusted OR, 1.016; $p = 0.001$) in unmatched subjects.

Next, propensity matching was used to identify the effects of RAS blockade excluding other influential factors. The results showed that no significant difference existed between the groups with respect to eGFR, hemoglobin level, or severe HF (Table 3). A further multiple regression analysis after propensity match-

Table 1. Patients' characteristics according to renin-angiotensin-system blocker use in unmatched subjects

Characteristic	RAS blockade (-) (n = 1,058)	RAS blockade (+) (n = 414)	p value
Age, yr	61.39 ± 11.40	64.56 ± 10.14	< 0.001
Dye volume, mL	184.17 ± 104.79	209.54 ± 106.39	< 0.001
Hemoglobin, mg/dL	13.50 ± 1.89	12.84 ± 1.67	< 0.001
eGFR, dL/min	82.33 ± 30.87	74.59 ± 28.82	< 0.001
Male sex	586 (55.4)	192 (46.4)	0.002
Severe heart failure	24 (2.3)	6 (1.4)	0.317
Current smoker	300 (28.4)	85 (20.5)	0.002
Diabetes mellitus	818 (77.3)	218 (52.7)	< 0.001

Values are presented as mean \pm SD or number (%).

RAS, renin-angiotensin-system; eGFR, effective glomerular filtration rate.

Table 2. Risk factors for contrast-medium-induced acute kidney injury identified through multiple logistic regression analysis in unmatched subjects

Variable	Unadjusted		Adjusted	
	OR (95% CI)	p value	OR (95% CI)	p value
RAS blockade	1.186 (0.89–1.580)	0.245	1.372 (1.003–1.877)	0.048
Age	0.996 (0.984–1.008)	0.512	1.027 (1.007–1.048)	0.007
Dye volume	0.997 (0.996–0.998)	< 0.001	0.997 (0.996–0.999)	0.001
Hemoglobin	0.932 (0.865–1.004)	0.065	0.899 (0.817–0.990)	0.031
eGFR	1.012 (1.008–1.016)	< 0.001	1.016 (1.007–1.025)	0.001
Male sex	1.204 (0.925–1.597)	0.168	0.773 (0.515–1.161)	0.215
Severe heart failure	6.112 (2.932–12.742)	< 0.001	12.454 (5.457–28.424)	< 0.001
Smoker	0.890 (0.656–1.208)	0.455	0.981 (0.679–1.418)	0.920
Diabetes mellitus	0.931 (0.696–1.246)	0.630	1.083 (0.781–1.502)	0.632

OR, odds ratio; CI, confidence interval; RAS, renin-angiotensin-system; eGFR, effective glomerular filtration rate.

ing showed that the adjusted OR for CIAKI increased significantly to 1.552 among those receiving RAS blockers (Table 4). Age, dye volume used, eGFR, and HF were also significant predictors of CIAKI in matched subjects.

DISCUSSION

Conflicting views exist regarding the effects of RAS blockers, such as ACEIs and ARBs, on CIAKI. In this study, we used propensity matching and multiple regression analysis to show that previous use of a RAS blocker significantly increased the risk of CIAKI.

Large-scale studies have shown that RAS blockade has beneficial effects on left ventricular systolic dysfunction, congestive HF, and prevention of the progression of diabetic nephropathy [14-18]. However, an acute rise in serum creatinine levels after the use of RAS blockers is frequently observed in clinical practice. Several factors have been suggested to explain this phenomenon. ACEIs reduce the pressure head from the afferent arterioles and lead to a reduction in intraglomerular pressure. Thus, the compensatory elevation of single-nephron GFR observed in renal insufficiency and diabetes is reduced during concurrent hypoperfusion and ACE inhibition [19]. Another explanation is related to renal autoregulation of pressure

Table 3. Patients' characteristics according to renin-angiotensin-system blocker use after propensity matching

Characteristic	RAS blockade (-)	RAS blockade (+)	p value
Number	376	376	
Age, yr	64.53 ± 10.25	64.18 ± 10.16	0.637
Baseline creatinine, mg/dL	0.87 ± 0.23	0.89 ± 0.24	0.198
Dye volume, mg/dL	195.48 ± 103.50	201.46 ± 105.66	0.433
Hemoglobin, mg/dL	12.91 ± 1.65	12.99 ± 1.64	0.508
eGFR, mL/min	73.82 ± 26.43	76.76 ± 28.73	0.145
Male sex	176 (48.5)	187 (51.5)	0.422
Severe heart failure	4 (40.0)	6 (60.0)	0.524
Current smoker	83 (49.7)	84 (50.3)	0.930
Diabetes mellitus	162 (50.0)	162 (50.0)	1.000

Values are presented as mean ± SD or number (%).

RAS, renin-angiotensin-system; eGFR, effective glomerular filtration rate.

Table 4. Effects of renin-angiotensin-system blockade on contrast-medium-induced acute kidney injury in matched subjects

Variable	Unadjusted		Adjusted	
	OR (95% CI)	p value	OR (95% CI)	p value
RAS blockade	1.552 (1.054-2.286)	0.026	1.556 (1.035-2.339)	0.034
Age	0.993 (0.975-1.012)	0.480	1.046 (1.015-1.079)	0.003
Dye volume	0.996 (0.994-0.998)	< 0.001	0.996 (0.994-0.998)	< 0.001
Hemoglobin	0.965 (0.860-1.084)	0.550	0.908 (0.780-1.055)	0.208
eGFR	1.015 (1.009-1.022)	< 0.001	1.025 (1.011-1.039)	0.001
Male sex	1.272 (0.866-1.848)	0.220	1.167 (0.648-2.100)	0.608
Severe heart failure	3.355 (0.933-12.065)	0.064	4.466 (1.157-17.243)	0.030
Current smoker	1.161 (0.742-1.816)	0.513	1.420 (0.821-2.458)	0.210
Diabetes mellitus	0.768 (0.519-1.137)	0.188	0.929 (0.610-1.415)	0.732

OR, odds ratio; CI, confidence interval; RAS, renin-angiotensin-system; eGFR, effective glomerular filtration rate.

through the nephrons [19-21]. Bilateral renal artery stenosis may also cause elevated serum creatinine levels following initiation of ACEI therapy.

The effect of RAS blockade on CIAKI incidence remains unclear. ACE-inhibitor therapy decreased the incidence of CIAKI in 71 diabetic patients after cardiac catheterization and in more than 7,000 patients with chronic kidney disease undergoing percutaneous coronary intervention [22,23]. Kiski et al. [2] examined the effects of ACEIs and ARBs on contrast-induced nephropathy (CIN); the study included 412 patients, among whom 269 patients were receiving RAS blockers. Although the study revealed no significant difference in age, serum creatinine, or left ventricular function between groups, the incidence of CIN was significantly higher in the RAS blockade group (11.9%) than in the untreated group (4.2%; $p = 0.001$). Toprak et al. [15] also showed that the ACEI captopril was a risk factor for developing CIAKI, whereas Gupta et al. [23] stated that captopril offered protection against CIN. However, both of these studies had limited statistical power due to small sample sizes, and did not account for confounding effects due to inclusion of diabetic patients [15,23]. Other studies into the effects of RAS blockade have included patients with chronic kidney disease [23] or failed to account for other important risk factors for CIAKI, such as baseline kidney function, contrast agent volume, and congestive HF. These limitations and differences in study design may explain conflicting reports as to the effect of RAS blockade on CIAKI.

To overcome these issues, we examined a broader range of potential confounders and used propensity score matching to correct for biases due to treatment recruitment. We observed significant differences in terms of age, dye volume, hemoglobin level, eGFR, gender, smoking status, and the incidence of diabetes between subjects receiving RAS blockade and those without. In order to clarify the effect of RAS blockade on CIAKI, we matched other risk factors using the propensity score method and found that RAS blockade increased the incidence of CIAKI in our multiple logistic regression analysis, with an adjusted OR of 1.556 ($p = 0.034$) (Table 4). A similar trend was observed among unmatched subjects (adjusted OR, 1.372; $p = 0.048$) (Table 2), and these results are consistent with

those of a recent study [24].

Several theories regarding the pathophysiology of CIAKI have been suggested. One theory states that contrast medium increases vasoconstriction at the corticomedullary junction in the kidney and reduces vasodilation due to a reduction in nitric oxide production, resulting in hypoxia and acute tubular necrosis [25]. Therefore, CIAKI can be principally classified as an ischemic acute kidney injury caused by the vasoconstrictive properties of contrast media. In addition, contrast media not only have a direct toxic effect on endothelial cells and renal tubules but also potentiate toxicity by reducing erythrocyte flexibility and activating leukocyte adhesion molecule, which facilitates the binding of leukocytes to endothelial cells. Contrast media also stimulate adenosine receptor A₁ and induce vasoconstriction of the afferent arterioles, resulting in renal ischemia [25].

Several risk factors can be inferred from these theories of CIAKI pathogenesis. One of the most significant risk factors for CIAKI is existing chronic renal disease. We found that elevated eGFR increased CIAKI risk with a relatively small but statistically significant OR (adjusted OR, 1.025) (Table 4), which is in contrast to previous reports of no effect [24,26]. However, it is possible that we detected a significant effect because we were better able to limit the confounding effect of chronic kidney disease by excluding patients with serum creatinine levels > 2.0 mg/dL. We furthermore used a continuous variable (eGFR) to account for kidney function, rather than a categorical variable like presence/absence of chronic kidney disease, which may have increased sensitivity. The volume of contrast medium used is also an important risk factor for CIAKI because the dye itself may cause vasoconstriction of renal tubular arterioles and direct tubular toxicity [27]. In our results, the use of less contrast medium in coronary angiography tended to increase CIAKI risk, but its OR was close to 1 (Table 4). In the baseline characteristics, contrast medium volume was lower in the CIAKI (+) group than in the CIAKI (-) group (data not shown). In clinical practice, cardiologists regulate the amount of contrast medium used during coronary angiography based on several factors. If patients show multiple risk factors for CIAKI, the cardiologist may reduce contrast dye volume to prevent CIAKI. Thus,

clinical judgments can also be a confounding factor in retrospective studies examining the effect of contrast medium volume on CIAKI. In addition, age, anemia, and congestive HF were significant risk factors for CIAKI in both matched and unmatched subjects (Tables 2 and 4), which is consistent with other studies [24,26,28].

Our study had several limitations. First, this study was conducted at a single center, although it involved a large population of more 1,400 patients. Second, this was an observational, rather than a randomized controlled, study. RAS blockade was not randomized and other risk factors differed between the RAS (-) versus RAS (+) groups. Because smoking is an important risk factor for coronary atherosclerosis, it would have been useful to analyze smoking status in more detail, although such information was not attainable given the retrospective nature of this study. To overcome these limitations, we used the propensity-score-matching method.

This study identified RAS blocking agents as a possible risk factor for CIAKI in angiocardiology patients. Although this study does not present sufficient evidence to justify halting the use of RAS blockers before coronary angiography, as has taken place in several institutes, our results demonstrate that clinicians should be aware of the risks of RAS blockade for CIAKI and exercise caution when necessary.

KEY MESSAGE

1. Angiocardiology have been increased to diagnosis and treat an ischemic heart disease and the use of contrast media has been linked to an acute kidney injury.
2. Renin-angiotensin-system (RAS) blockers are used to control hypertension and subsequent complications in at-risk patients.
3. The impacts RAS blockade on contrast-medium-induced acute kidney injury (CIAKI) have been controversial. In this study, the incidence of CIAKI was increased in patients treated with RAS blockers.
4. Clinicians should be aware of the risks of RAS blockade for CIAKI.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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