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Original article

Effect of contrast-induced nephropathy on cardiac outcomes after use of nonionic isosmolar contrast media during coronary procedure

Jae Yeong Cho (MD), Myung Ho Jeong (MD, PhD)*, Su Hwan Park (MS), In Soo Kim (MS), Keun Ho Park (MD), Doo Sun Sim (MD), Nam Sik Yoon (MD), Hyun Ju Yoon (MD), Hyung Wook Park (MD), Young Joon Hong (MD), Ju Han Kim (MD), Youngkeun Ahn (MD), Jeong Gwan Cho (MD), Jong Chun Park (MD), Jung Chaee Kang (MD, PhD)

The Heart Research Center of Chonnam National University Hospital, Cardiovascular Research Institute of Chonnam National University, 671 Jaebongro, Dong-gu, Gwangju 501-751, Republic of Korea

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Summary Contrast-induced nephropathy (CIN) has been increasing and seems to be associated with clinical outcomes in ischemic heart disease. This study aimed to assess the incidence, predictors, and cardiac outcomes of CIN when nonionic isosmolar contrast media (iodixanol, Visipaque®, GE Healthcare, Cork, Ireland) was used. Between January 2005 and July 2008, 510 patients (69.2 ± 9.0 years of age, 384 men) undergoing diagnostic coronary angiography (CAG) or percutaneous coronary intervention (PCI) were divided into two groups according to the development of CIN (CIN group: $n = 74$; non-CIN group: $n = 436$). CIN developed in 74 patients (14.5%). They were more likely to have diabetes (55.4% vs. 42.9%, $p = 0.045$), decreased left ventricular ejection fraction (LVEF) (50.1 ± 12.6% vs. 57.7 ± 13.9%, $p < 0.001$), and lower baseline hematocrit level (32.4 ± 5.3% vs. 36.6 ± 5.5%, $p < 0.001$). Multiple logistic regression analysis revealed baseline hematocrit (odds ratio 0.900, 95% confidence interval 0.851—0.952, $p < 0.001$), decreased LVEF (odds ratio 0.967, 95% confidence interval 0.949—0.986, $p = 0.001$), and baseline creatinine level (odds ratio 2.317, 95% confidence interval 1.252—4.286, $p = 0.007$) as independent predictors of CIN. At 1-year follow-up, patients with CIN were found to have more adverse outcomes than without CIN in Cox proportional hazards analysis (hazard ratio 13.068, 95% confidence interval 2.425—70.434, $p = 0.003$). CIN was mostly associated with baseline creatinine level rather than CM amount using nonionic isosmolar CM. We found that patients with CIN had worse event-free survival than patients without CIN after multifactorial adjustment.

* Corresponding author. Tel.: +82 62 220 6243; fax: +82 62 228 7174.
E-mail addresses: myungho@chollian.net, myungho@chol.com (M.H. Jeong).

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Introduction

Contrast-induced nephropathy (CIN) has been generally characterized by an increase in serum creatinine (Cr) concentration of at least 0.5 mg/dL or by a relative increase of at least 25% from baseline after use of contrast media (CM) [1]. To date, various predictive factors for CIN have been reported. They are grouped into two major categories: patient related and non-patient related factors. The former refers to chronic kidney disease, diabetes mellitus, urgent procedure, intra-aortic balloon pump, congestive heart failure, age, hypertension, low hematocrit, hypotension, and low left ventricular ejection fraction, and the latter consists of high osmolar CM, ionic CM, contrast viscosity, and contrast volume [2]. Since it was repeatedly reported that CIN is associated with prolonged hospitalization and increased morbidity and mortality [3–7], minimizing risk factors for CIN should be done. It can be achieved initially by avoiding high osmolar or ionic CM, the easily modifiable risk factor.

Contrary to general expectations, there were a few studies about using nonionic isosmolar CM. A former study suggested that isosmolar, nonionic CM may be superior to others in a randomized controlled trial [8]. However, several subsequent studies failed to confirm this. Even a large-scale study strongly suggested that an isosmolar CM more often causes clinically relevant renal failure than a low-osmolar contrast agent [9]. Moreover, various clinical settings according to certain prophylaxis or underlying diseases have resulted in different outcomes from those derived from conventional risk factors [10]. The type of CM could not be the exception. Hence, we should be aware of the specific risk factors for CIN from isosmolar CM use and accordingly, reduce the risk of CIN. The present study was aimed to investigate the incidence, predictors, and long-term cardiac outcomes of CIN with use of nonionic isosmolar CM.

Materials and methods

Study design and sample

Between January 2005 and July 2008, 510 patients (69.2 ± 9.0 years of age, 384 men) undergoing diagnostic coronary angiography or percutaneous coronary intervention at Heart Center of Chonnam National University Hospital, Gwangju, South Korea were analyzed retrospectively.

Patients were divided into two groups according to the development of CIN (CIN group: $n = 74$; non-CIN group: $n = 436$). Of the 510 subjects, 487 were followed up for 1-year and we analyzed long-term clinical outcomes in those patients.

Definitions

CIN was defined as an increase of $\geq$25% or $\geq$0.5 mg/dL in pre-procedure serum Cr after procedure. Cr level was measured at baseline and daily for 3 days after the procedure for most of the patients. Two daily measurements of Cr were made in patients undergoing only coronary angiography as they were discharged earlier. Additional measurements were performed in all cases with deterioration of renal function after contrast exposure. The Cr clearance (CrCl) was calculated by applying the Cockroft–Gault formula [11] to the baseline Cr concentration values: CrCl = [(140-age) $\times$ weight]/[serum Cr $\times$ 72], with female gender adjustment ($CrCl_{female} = CrCl \times 0.85$).

The contrast volume was corrected in relation to underlying renal function. Maximum contrast dose (MCD) was calculated by the following formula [12]: Maximum contrast dose = [5 mL $\times$ weight (kg)]/baseline serum Cr. Then we calculated CM dose/MCD ratio.

We also evaluated hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or receiving antihypertensive drugs), diabetes mellitus (fasting glucose level $\geq$ 126 mg/dL or random blood glucose level $\geq$ 200 mg/dL), current smoking habit, and hyperlipidemia (total cholesterol level $\geq$ 240 mg/dL, triglyceride level $\geq$ 150 mg/dL, or receiving hyperlipidemia medication).

Initial management

Before elective procedure, normal saline was given intravenously at a rate of 1 mL/kg/h for 24 h. When emergency percutaneous coronary intervention was needed for ST elevation myocardial infarction patients, they received high dose of aspirin (300 mg) and clopidogrel (300 mg) and continued to take low-dose aspirin (100 mg) and clopidogrel (75 mg) after the procedure. In addition the patients received a bolus of 5000 U heparin in the emergency ward, followed by continuous infusion of heparin. Target lesions were predilated using conventional angioplasty balloons followed by stent implantation. After procedures, physiologic saline was given intravenously at a rate of 1 mL/kg/h for 12 h. In patients with left ventricular dysfunction or overt heart failure, the hydration rate was reduced to 0.5 mL/kg/h.

Clinical variables

Peripheral blood samples were obtained using direct venipuncture. The blood samples were centrifuged, and serum was removed and stored at $-70\,^{\circ}C$ until the assay could be performed. The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by standard enzymatic methods. High-sensitivity C-reactive protein was analyzed turbidimetrically with sheep antibodies against human C-reactive protein. This has been validated against the Dade–Behring method. Serum amino-terminal pro-brain natriuretic peptide was measured using an electrochemiluminescence sandwich immunoassay method with an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

Left ventricular ejection fraction was usually measured in all patients on admission. Especially for patients with acute myocardial infarction, the measurement was done in either emergency room using a portable echocardiography system (Acuson Cypress, Acuson, Mountain View, CA, USA) or cardiac catheterization laboratory using an echocardiography system (Acuson Sequoia). Conventional coronary angiography was performed using a digital flat panel fluoroscopy (Phillips, Eindhoven, The Netherlands) via femoral or radial

approaches applying nonionic isosmolar contrast material (Visipaque® 320, GE Healthcare, Cork, Ireland). A minimum of four orthogonal views were obtained.

End points

The primary outcome for this analysis was composite of 1-year adverse cardiac events. The adverse cardiac event was defined as composite of cardiac death, non-cardiac death, and revascularization of coronary artery.

Statistical analysis

Continuous variables with normal distributions are presented as mean ± SD and were compared with the use of the Student's *t*-test or Mann—Whitney *U*-test if normality assumption was violated. Categorical variables were compared with the use of the Chi-square test or Fisher's exact test, where appropriate. Multivariate logistic regression analysis was used to identify correlates of CIN. The response variable was the development of CIN defined as an increase in Cr concentration of ≥25% or ≥0.5 mg/dL. Models were developed with stepwise techniques and by consideration of variables that were clinically relevant. Odds ratios and their two-sided 95% confidence intervals are reported, and significance was determined by the position of the 95% confidence interval. A confidence interval not including 1 was considered statistically significant. Cox proportional hazards regression was used to examine the association between multiple variables and the long-term adverse outcomes. Then, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) comparing event-free survival rates between CIN and non-CIN group using the Cox proportional hazard method. We determined that the proportional hazard assumption was satisfied by examining plots of the log-negative-log of the within-group survivorship functions vs. log-time as well as comparing Kaplan—Meier with Cox survival curves. Statistical analysis was done with the Statistical Package for Social Sciences software, version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corp., Redmond, WA, USA).

Results

Patient characteristics

Baseline characteristics of the two groups are presented in Table 1. There were notable differences between patients with and without CIN. Patients with CIN were older (71.2 ± 7.9 vs. 68.9 ± 9.2 years, $p = 0.042$), more likely to be women (63.5% vs. 77.3%, $p = 0.011$), have diabetes (55.4% vs. 42.9%, $p = 0.045$), and have lower body mass index (22.9 ± 2.6 vs. 24.0 ± 3.3 kg/m^2, $p = 0.007$). Patients with CIN were also more likely to have lower left ventricular ejection fraction (50.1 ± 12.6% vs. 57.7 ± 13.9%, $p < 0.001$), cardiogenic shock (47.1% vs. 12.2%, $p = 0.002$), and a trend toward a greater amount of CM use (138.3 ± 64.7 vs. 127.4 ± 72.8 mL, $p = 0.227$). But, there was a significant dif-

Table 1 Baseline characteristics.

	CIN group ($n = 74$)	Non-CIN group ($n = 436$)	p
Age (years)	71.2 ± 7.9	68.9 ± 9.2	0.042
Male sex	47(63.5%)	337(77.3%)	0.011
Body mass index (kg/m^2)	22.9 ± 2.6	24.0 ± 3.3	0.007
Hypertension	59(79.7)	299(68.6)	0.052
Diabetes mellitus	41(55.4)	187(42.9)	0.045
Hyperlipidemia	14(18.9)	54(12.4)	0.126
Smoking	27(36.5)	146(33.5)	0.614
Old myocardial infarction	4(5.4)	39(8.9)	0.311
Stable angina	8(10.8)	102(23.4)	0.015
Unstable angina	21(28.4)	159(36.5)	0.178
Acute myocardial infarction	41(55.4)	136(31.2)	<0.001
Left ventricular ejection fraction (%)	50.1 ± 12.6	57.7 ± 13.9	<0.001
Cardiogenic shock	47.1%	12.2%	0.002
Amount of contrast medium used (mL)	138.3 ± 64.7	127.4 ± 72.8	0.227
Maximum contrast dose (mL)	186.9 ± 42.3	219.1 ± 50.9	<0.001
Contrast medium used/Maximum contrast dose ratio	0.79 ± 0.45	0.63 ± 0.41	0.002
Baseline hematocrit (%)	32.4 ± 5.3	36.6 ± 5.5	<0.001
Baseline creatinine (mg/dL)	1.72 ± 0.49	1.52 ± 0.33	0.001
Creatinine clearance (mL/min)	33.0 ± 10.1	42.1 ± 13.7	<0.001
Total cholesterol (mg/dL)	161.3 ± 46.8	178.6 ± 44.5	0.165
Triglyceride (mg/dL)	112.4 ± 57.0	112.6 ± 57.0	0.988
High-density lipoprotein cholesterol (mg/dL)	41.5 ± 13.3	44.5 ± 13.7	0.374
Low-density lipoprotein cholesterol (mg/dL)	99.9 ± 41.0	115.1 ± 39.2	0.168
High-sensitivity C-reactive protein (mg/dL)	2.59 ± 2.02	3.61 ± 4.25	0.151
Amino-terminal pro-brain natriuretic peptide (mg/dL)	12843.1 ± 10915.7	4636.5 ± 7574.5	0.010

Data are presented as the number (%) of patients or mean ± SD. CIN, contrast-induced nephropathy.

Table 2 Procedural characteristics.

	CIN group ($n=74$)	Non-CIN group ($n=436$)	p
Culprit lesion			
Left main	6(8.1)	16(3.7)	0.263
Left anterior descending artery	23(31.1)	182(41.7)	0.215
Left circumflex artery	17(23.0)	63(14.5)	0.188
Right coronary artery	29(39.2)	177(40.6)	0.827
Lesion location			
Proximal	33(44.6)	220(50.5)	0.503
Middle	24(32.4)	141(32.3)	0.923
Distal	16(21.6)	73(16.7)	0.449
Multivessel disease	13(17.6)	50(11.5)	0.212
Pre-TIMI flow			0.714
0	34(46.0)	213(48.9)	
1	9(12.2)	72(16.5)	
2	7(9.5)	8(1.8)	
3	23(31.1)	143(32.8)	
Lesion type[a]			0.530
A	34(46.0)	214(49.1)	
B1	8(10.8)	53(12.2)	
B2	15(20.3)	88(20.2)	
C	17(23.0)	81(18.6)	
Stent profile			
Stent diameter (mm)	3.1 ± 0.4	3.2 ± 2.0	0.761
Stent length (mm)	24.5 ± 7.3	25.3 ± 6.69	0.537

Data are presented as the number (%) of patients or mean $\pm$ SD.
[a] Lesion type according to American College of Cardiology/American Heart Association; CIN, contrast-induced nephropathy; TIMI, thrombolysis in myocardial infarction.

ference in CM used/MCD ratio (0.79 ± 0.45 vs. 0.63 ± 0.41, $p=0.002$).

With regard to initial clinical diagnosis, more than half of the patients with CIN were diagnosed with acute myocardial infarction (55.4% vs. 31.2%, $p<0.001$), while there were fewer patients with stable angina (10.8% vs. 23.4%, $p=0.015$).

In patients with CIN, baseline Cr level was higher (1.72 ± 0.49 vs. 1.52 ± 0.33 mg/dL, $p=0.001$) and accordingly, CrCl was lower (33.0 ± 10.1 vs. 42.1 ± 13.7 mL/min, $p<0.001$). Also, hematocrit (32.4 ± 5.3 vs. 36.6 ± 5.5%, $p<0.001$) and mean serum glucose level was lower (159 ± 48 vs. 196 ± 118 mg/dL, $p=0.028$). But, there were no significant differences in lipid profiles and inflammatory markers between the two groups.

Procedural findings are summarized in Table 2. No notable significant procedural differences between subjects with and without CIN were found. There were only trends toward more multivessel diseases and complicated lesions in patients with CIN.

Predictors of CIN

Multivariate logistic regression analyses of the association between CIN and multiple parameters are presented in Table 3. Univariable analysis was first conducted to identify potential predictors for CIN. All variables with $p<0.2$ in univariable analysis (age, sex, body mass index, diabetes mellitus, left ventricular ejection fraction, baseline creatinine level, baseline hematocrit, and CM used/MCD ratio) were tested for multivariable analysis.

In multivariate analysis, baseline hematocrit, left ventricular ejection fraction, and baseline Cr level were predictors of CIN. The most powerful parameter to predict CIN was baseline serum Cr level (odds ratio 2.375, 95% confidence interval 1.273—4.428, $p=0.007$), but the amount of CM failed to be an independent predictor of CIN.

Clinical outcomes between groups

The clinical outcomes are summarized in Table 4. There were more in-hospital deaths in patients with CIN. Also, there were significantly more hospital days for patients with CIN than for patients without CIN. Patients with CIN showed higher mortality at 1-year follow-up. Composite adverse outcomes in the CIN group were greater than that of the non-CIN group (23.2% vs. 13.2%, $p=0.029$), especially among the subset of outcomes, cardiac death rate was greater in the CIN group (14.5% vs. 2.6%, $p<0.001$).

In Cox proportional hazards regression analysis, patients with CIN showed worse cardiac outcomes than patients without CIN in event-free survival curve adjusted for multiple

Table 3 Independent predictors of contrast-induced nephropathy.

	Odds ratio	95% confidence interval	*p*
Baseline hematocrit	0.900	0.851—0.952	<0.001
Left ventricular ejection fraction	0.967	0.949—0.986	0.001
Baseline creatinine level	2.317	1.252—4.286	0.007
Sex	1.337	0.726—2.464	0.351
Age	1.018	0.983—1.053	0.315
Dose of contrast medium used/maximum contrast dose ratio	1.011	0.509—2.009	0.975
Body mass index	0.961	0.878—1.052	0.390
Diabetes mellitus	1.208	0.688—2.121	0.510

Table 4 Clinical outcomes between patients with and without contrast-induced nephropathy (CIN).

	CIN group ($n = 74$)	Non-CIN group ($n = 436$)	*p*
In-hospital outcomes			
In-hospital death	6(8.1)	3(0.7)	<0.001
Hospital day (days)	14.7 ± 12.1	9.1 ± 15.2	0.003
One-year adverse outcomes	($n = 69$)	($n = 418$)	
All-cause death	11(15.9)	17(4.1)	0.001
Cardiac death	10(14.5)	11(2.6)	<0.001
Non-cardiac death	1(1.4)	6(1.4)	1.000
Revascularization	5(7.3)	38(9.1)	0.705
Composite	16(23.2)	55(13.2)	0.029

Data are presented as the number (%) of patients or mean $\pm$ SD.

risk factors (hazard ratio 13.068, 95% confidence interval 2.425—70.434, $p = 0.003$) (Fig. 1).

Discussion

The present study indicated that even nonionic isosmolar CM could cause CIN to a certain degree and also the patients with CIN had different risk factors. The independent predictors of CIN after using nonionic isosmolar CM were baseline hematocrit, left ventricular ejection fraction, and baseline Cr level. In addition, patients with CIN showed worse long-term cardiac outcomes than patients without CIN in Cox proportional hazard regression analysis.

The incidence of CIN was 14.5% in the present study. Some studies showed lower incidences of CIN than our study [7,8,13—15] and some were similar [5,16]. But, there is a wide variation in reported rates of CIN in the real world. This was thought to be caused by lack of a standardization, timing of Cr measurement, baseline characteristics, and type of CM used [17].

Not all studies have demonstrated a contrast dose-dependent risk of CIN. Lautin et al. [18] reported that the effects of dehydration and increased volume of contrast medium on the incidence of CIN were not clear. Since we examined patients undergoing coronary angiography as well as percutaneous coronary intervention, the amount of CM used was rather smaller compared with the data from McCullough et al. (247.8 ± 113.0 vs. $129.0 \pm 71.7\,cm^3$) [5]. Moreover, there were 136 patients out of 510 with acute myocardial infarction, which accounted for only 31.2% of the total population. But CIN occurred in 14.5% of total patients, which is exactly the same incidence as in the study by McCullough et al. [5]. It might be suggested that the amount of CM is not associated with CIN by the results above. However, the dose of CM should not be excluded as a risk factor of CIN. Rudnick et al. [19] reported that baseline serum creatinine, male gender, diabetes, volume of contrast agent, and renal insufficiency were independently related to the risk of nephrotoxicity. Cigarroa et al. [12] reported that diabetic patients had a high incidence of contrast nephropathy, particularly when they receive an excessive amount of contrast. Nozue et al. [20] reported that the contrast medium volume to estimated glomerular filtration rate ratio was a significant independent predictor of CIN. Nevertheless, several studies reported that amount of CM had no effect on increase of CIN any more when prophylactic therapy such as adequate intravenous fluid was given or the patients had better renal function [21]. In that sense, low osmolality of contrast media might also be one of the prophylactic measures that can neutralize the dose-related increase of CIN. Likewise, risk factors and outcomes of CIN could vary according to osmolality of contrast media.

In-hospital mortality in our study was relatively low. Studies so far have not shown consistent results of in-hospital mortality of patients with CIN. McCullough et al. [5] reported 7.1% in-hospital mortality in patients with acute renal failure. Rihal et al. [7] reported 22% in-hospital mortality and 12.1% 1-year mortality. We had in-hospital mortality of 8.1% and 1 year mortality of 15.9% in patients with CIN. In terms of baseline characteristics, the number of patients diagnosed with acute coronary syndrome was relatively low in this

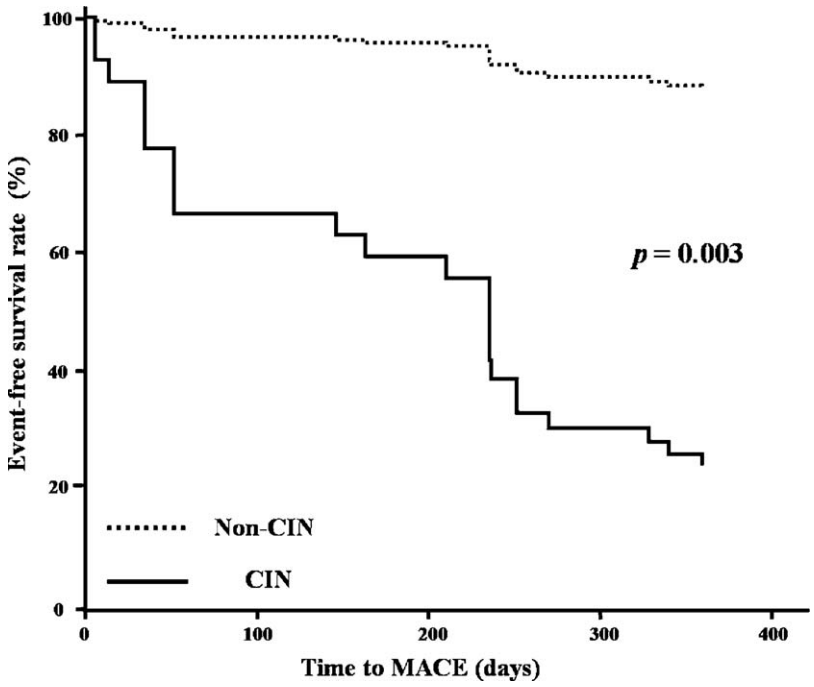

Figure 1 Multifactorially adjusted event-free survival curve according to patient groups with or without contrast-induced nephropathy. CIN, contrast-induced nephropathy; MACE, major adverse cardiac events.

study. With respect to procedural characteristics, our results have shown no significant differences in number of patients with multivessel disease. Some other studies have shown that patients with CIN are more likely to have multivessel disease [22,23]. Since we included patients undergoing coronary angiography as well as percutaneous coronary intervention, the absolute incidence of multivessel disease seemed to be lower than other studies.

The present study has several limitations. First, it was limited because of its retrospective nature and was therefore subject to the limitations pertinent to this type of clinical investigation. Not all data for variables suggested as a risk factor of CIN so far were available. Second, this was a single-center study and thus the result of this study should be verified by further prospective investigation. Third, there might be some variations of definition of CIN. The standardization of definition of CIN is needed. Fourth, operators' effort to reduce CIN might influence the outcomes with the information of patients' baseline characteristics before procedures. Fifth, the relatively small sample size might have resulted in overestimation of incidence of adverse outcomes, limited statistical power, and selection bias.

In conclusion, even though we used nonionic isosmolar CM during coronary procedures, the occurrence of CIN occurred to a certain degree. Predictors of CIN after use of nonionic isosmolar CM during coronary angiography or percutaneous coronary intervention were baseline Cr level, decreased baseline hematocrit, and decreased left ventricular ejection fraction. Patients with CIN showed worse long-term cardiac outcomes than patients without CIN in Cox proportional hazard regression analysis. These results support the idea that we have to prevent CIN because it is associated with 1-year mortality.

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