

Contrast-Induced Nephropathy in Patients Undergoing Elective Coronary Angiography: Incidence and Risk Factors

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Abstract: Contrast-Induced Nephropathy (CIN) is a considerable complication in cardiac procedures. Several conditions for CIN have been identified after Coronary Angiography (CA). The purpose of this study was to assess the incidence and clinical predictors of CIN 24 h after Coronary Angiography. A total of 1,137 consecutive patients with coronary artery syndrome undergoing CA were prospectively enrolled the study. Serum creatinine (Cr) at baseline and 24 h after CA, as well as demographic and clinical characteristics of patients were measured. Contrast-induced nephropathy was defined as a rise in Cr ≥ 0.3 mg/dl after CA. Univariable and multivariable logistic regression analysis were performed to identify independent predictors of CIN. The overall incidence rate was 56 (4.9%) in total study population. In multivariate analysis, baseline Cr > 1.5 (odds ratio [OR] 4.8, 95% confidence interval [CI] 1.04 to 8.3; $P < 0.001$), Contrast volume > 100 mL (OR 3.4, 95% CI 0.7 to 8.1; $P < 0.002$), Baseline GFR < 30 (OR 14.2, 95% CI 8-2; $P < 0.000$); Baseline GFR 30-60 (OR 8.7, 95% CI 2.3 13.8; $P < 0.000$) were predictors for CIN. CIN was more frequent in older patients, with higher serum creatinine level and Greater usage of contrast media and diuretic. N-acetylcysteine (NAC) and hydration cannot prevent the occurrence of CIN.

Key words: Contrast nephropathy, coronary angiography, contrast media.

1. Introduction

Acute renal failure (ARF) after coronary angiography is often attributed to Contrast-induced nephropathy (CIN) [1, 2]. Recent evidence suggests that CIN is associated with longer hospitalization [3], permanent renal failure [1, 2] and increased mortality [4-6]. Appropriate identification of at risk patients may reduce the duration of hospitalization and morbidity after CA [7]. Several risk factors are attributed to CIN, including: advancing age, volume of contrast medium, previous chronic renal failure, diabetes, reduced left ventricular systolic function, concomitant use of nephrotoxic drugs, and periprocedural hemodynamic instability [8-10]. Special conditions in cardiac procedures may

predispose renal injury like predominant vascular atherosclerosis and hypotension [7]. Several studies assessed individual risk factors and cumulative effect of these risk factors on renal function in patients with acute myocardial infarction (AMI) [1, 10, 11]. Some studies assess the probability of renal insufficiency after PCI with the development of risk score models [10-12]. Although, the results of the various study were different and every study suggested different factors influence on occurrence of CIN. Monthly, a large number of coronary angiography have been conducted in referral heart centers of Guilan University of Medical Sciences, so, determining the frequency of CIN and its related factors seems to be necessary.

The purpose of the present prospective study was to determine the incidence of CIN and associated demographic and clinical factors for developing CIN

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after CA in patients with acute coronary syndrome in university teaching hospital of Guilan province, north of Iran.

2. Patients and Methods

2.1 Study Population and Design

Between September, 2013, and August, 2014, we enrolled all patients with coronary artery syndrome admitted to Dr Heshmat hospital, the referral cardiovascular hospital of Rash, Guilan province of Iran who were treated with elective CA. Patients with GFR < 30 and candidate for dialysis as well as history of drug induced nephrotoxicity within the past two weeks such as non steroidal anti inflammatory drugs (NSAID), angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEI) and diuretic were excluded. Diabetic patients had been discontinued metformin treatment two days before CA. Variables included demographic parameters, a detailed history of cardiovascular disease and co-morbidities, procedural details (dose of contrast medium used and prophylactic measures to prevent the development of CIN for each patient) were recorded. The decision to implement renal prophylactic measures as well as the type of these measures (N-acetylcysteine and hydration) was left to the discretion of the physicians caring for the patient.

Study design was approved by the ethics committee of the Interventional cardiovascular research center (ICRC) of Guilan University of Medical Science (GUMS) (Project number: 92040883), and written informed consent (per the Helsinki declaration) was obtained from each participant.

2.2 Coronary Angiography

Coronary Angiography was performed by an interventional team, according to standard clinical practice [13]. Type of contrast agent and contrast dose, angiography technique, and supportive pharmacologic therapies were based on the decision of the interventional cardiologist.

2.3 Outcome and Data Measurements

The study outcome was contrast-induced nephropathy, defined as an absolute serum creatinine increase 0.3 mg/dl or a relative increase in serum creatinine 50% that occurred within 24 h after coronary angiography [14]. The frequency of CIN was calculated using pre- and Post-procedural serum creatinine measurements after 24 h. Preprocedural serum creatinine level and the glucose level were obtained closest to the time of coronary angiography during hospitalization. Creatinine clearance was calculated by applying the Cockcroft-Gault formula to the Cr [15].

2.4 Statistical Analysis

Results are reported as the mean value (SD) for continuous data and as absolute values and percentages for categorical data. Frequency of CIN was calculated in the entire sample. Comparison of continuous variables was compared by means of t test. Chi-square tests were used for comparison of categorical variables. Multivariable logistic regression models were subsequently developed to evaluate the association between patient's condition and CIN. Patient characteristics and other risk factors identified in univariable logistic regression as predictors of CIN (at a level of significance of $P < 0.05$), were entered into the models. Risk factors included demographic factors, comorbidities, and laboratory values, medications during hospitalization, contrast volume and preprocedural GFR. All comparisons were carried out on a two-tailed basis. Statistical analysis was carried out with the SPSS (version 16) and $P < 0.05$ was considered statistically significant. Ninety-five percent significant intervals (CI) for the proportions were calculated.

3. Results

3.1 Baseline Characteristics and Incidence of CIN

A total of 1,137 patients (633 men, 504 women; mean age 59.5 ± 1.5 years) were included in this

study. Diabetes and hypertension were present in 339 (29.8%) and 458 patients (40.3) respectively. The mean creatinine for all study patients at baseline was 0.98 (0.3) mg/dl. More than fifty percent of patients had reported serum creatinine was greater than mean. Overall, 56 patients (4.9%) developed CIN after coronary angiography. Mean creatinine in patients with CIN increased statistically significant from 1.2 ± 0.9 mg/dl at baseline to 1.8 ± 1.07 mg/dl, while patients without CIN experienced no significant change in serum creatinine (baseline: 0.9 ± 0.24 mg/dl; post-PCI: 1.01 ± 0.23 mg/dl). The mean volume of contrast material administered was 103 ± 30 ml.

Table 1 shows the baseline clinical and procedural characteristics of patients who developed CIN and of those who did not present this complication after CA. Patients developing CIN were older, higher baseline Cr value. In addition, they received a higher volume of the contrast agent during PCI than patients without CIN. When creatinine clearance was estimated, 13 (1.1%) and 165 (14.5) of the 1,137 patients had renal insufficiency (< 30 mL/min and 30-60, respectively). Of 13 patients with GFR < 30, 3 (23.1%) and of the 165 patients with GFR 30-60 mL/min, 13 (7.9%) developed CIN. In contrast, of the 959 patients with a baseline GFR value > 60 mL/min, only 40 (4.2%) developed CIN after PCI ($P < 0.001$). The medications taken by both groups were similar with the exception of diuretics, which were more common in the CIN group. Presence of hypertension, heart failure and diabetes mellitus were similar in both groups. Approximately 15.5% of patients received hydration with normal saline. Of them, 16 (9 %) developed CIN which was similar in cases without baseline hydration 45/959 (4.7%) ($P = 0.45$). No severe renal failure after intervention was seen in the study participants.

3.2 Univariable Analysis

Variables associated with CIN at 48 h in univariable

logistic regression models are shown in table 2. A total of 16 demographic, clinical, angiographic variables were studied. The five significantly associated variables included age > 60 years (OR 1.2, 95% CI 0.2-7.3; $P < 0.001$), baseline creatinine levels ≥ 1.5 mg/dl (OR 3.32, 95% CI 1.2-8.8; $P < 0.017$), pre-existing renal insufficiency: GFR < 30 as well as GFR 30 = 60, (OR 6.8, 95% CI 1.8-26; $P < 0.004$, OR 1.9, 95% CI 1.02-3.7; $P < 0.04$, respectively), volume contrast use ≥ 100 ml (OR 1.6, 95% CI 0.98-0.99; $P < 0.01$), and diuretics (OR 1.4, 95% CI 0.2-0.8; $P < 0.01$).

In multivariate analysis, the following variables remained significant independent correlates of CIN: baseline Cr > 1.5 (odds ratio [OR] 4.8, 95% confidence interval [CI] 1.04 to 8.3; $P < 0.001$), Contrast > 100 mmL (OR 3.4, 95% CI 0.7 to 8.1; $P < 0.002$), Baseline GFR < 30 (OR 14.2, 95% CI 8-2; $P < 0.000$); Baseline GFR 30-60 (OR 8.7, 95% CI 2.3 13.8; $P < 0.000$).

4. Discussion

We prospectively collected characteristics of a large of patients who underwent Coronary Angiography to assess the incidence of the CIN and its associated factors. CIN occurred in 4.9% of our study population at 24 h post CA. Gaetano M. De Ferrari et al showed the frequency of CIN after primary PCI in ST-segment elevation myocardial infarction (STEMI) was 5.6% [16]. Some studies showed higher incidences of CIN than our study like 10.2%-19% [1, 13, 17, 18] and some were similar [16, 19]. In our study, baseline creatinine levels in patients were experienced CIN were higher than patients without CIN. In fact patient with pre-existing renal insufficiency, especially patients with GFR < 30, 5 times more reported CIN than cases with GFR > 60. The odds of CIN in this group of study population about 14 times are higher than cases with GFR > 60. This is in line with the results of several studies that established our findings [20, 21]. Peter A. McCullough [22] in a review article mentioned that reduced glomerular filtration at

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Table 1 Baseline and clinical characteristics of the study patients.

Variable	All patients (N = 1,137)	CIN (n = 56)	No CIN (n = 1,081)	P value
Age (yrs)	59.5 (10.9)	62.3 (1.1)	59.3 (1.08)	0.09
Men, N (%)	633 (55%)	34 (60.7)	599 (55.4)	0.4
Diabetes	339 (29%)	19 (33.9)	320 (29.6)	0.4
Hypertension	4,589 (40%)	19 (33.9)	439 (40.6)	0.3
Heart Failure diagnosis	189 (16%)	14 (25)	175 (16.2)	0.08
MI	129 (9%)	7 (12.5)	122 (11.3)	
UA	793 (69%)	35 (62.5)	758 (70.1)	
NSTMI	215 (0.18)	14 (25)	201 (18.6)	
Contrast volume, mean (SD) (mL)	103 (30)	103.5 (30.8)	92.8 (31.7)	0.01*
Baseline Cr, mg/dl, mean (SD)	0.99 (0.32)	1.2 (0.99)	0.98 (0.24)	0.02*
Baseline BS	135 (62)	135 (62)	128 (57)	0.4
Baseline Hb, g/dl	13.6 (1.7)	13.3 (1.6)	13.6 (1.7)	0.3
ACE Inhibitor (n)	859 (75%)	43 (76.8)	816 (75.6)	0.8
Beta blocker (n)	925 (81%)	48 (85.7)	877 (81.2)	0.3
Diuretic, n (%)	189 (16%)	8 (14.1)	181 (8.3)	0.01*
NAC, n (%)	180 (15%)	9 (16)	171 (15.8)	0.31
Hydration infusion Rate, n (%)	177 (15.5)	16 (28)	45 (4)	0.01*
GFR (mL/min)				0.001*
< 30	13 (1.1%)	3 (5.4)	10 (9)	
31-60	185 (16%)	13 (23.2)	152 (14.1)	
> 61	959 (84%)	40 (71)	919 (85.4)	

CIN: contrast induced nephropathy; MI: myocardial infarction; UA: unstable angina; NSTMI: none ST elevation myocardial infarction; Cr: creatinine; BS: bold sugar; Hb: hemoglobin; ACE: Angiotensin converting enzyme; NAC: N-acetylcysteine; GFR: glomerular filtration rate.

Table 2 Univariable logistic regression of baseline, clinical, angiographic and procedural characteristics in the study patients.

Variables	Incidence of CIN (%)	Exp (B)/OR	95% CI	P value
Age > 60	6.5	1.2	0.2-7.3	0.001
Baseline Cr > 1.5	13.9	3.32	1.2-8.8	0.017
Contrast > 100 mml	5.3	1.6	0.98-0.99	0.01
Receive diuretic	8.4	1.4	0.2-0.8	0.01
Baseline GFR				
< 30	23	6.8	1.8-26	0.004
30-60	7.9	1.9	1.02-3.7	0.04

CIN: contrast induced nephropathy; OR: odds ratio; CI: confidence interval; GFR: glomerular filtration rate.

Table 3 Multivariable logistic regression of variables for CIN in the study patients.

Variables	Model coefficient (b value)	OR	95% CI	P value
Age > 65	2.1	1.4	0.09-6.9	0.021
Baseline Cr > 1.5	1.7	4.8	1.04- 8.3	0.001
Contrast > 100 mml	1.3	3.4	0.7-8.1	0.002
Baseline GFR				
< 30	4.9	14.2	8-21	0.000
30-60	2.9	8.7	2.3-13.8	0.000

CIN: contrast induced nephropathy; OR: odds ratio; CI: confidence interval; Baseline GFR: glomerular filtration rate.

baseline (GFR < 60 mL/min) is the single most important risk predictor for CIN, and should be a concern for preventive measures. Similarly, Michael W *et al.* [23] designed a prospective study to evaluate incidence and risk factors of CIN after cardiac catheterization in elderly patients. They found a high level of creatinine at baseline an independent risk factor for renal dysfunction.

According to multivariate logistic regression analysis, we detected the odds of CIN 24 h after CA in cases with baseline creatinine > 1.5 was approximately 5 times greater than in the study population with Cr < 1.5.

Our study revealed that old age and increased volume of contrast medium may enhance the occurrence of CIN after Coronary Angiography, in agreement with previously published evidence [10, 12, 13, 24]. The present study failed to illustrate the predictive effect of some factors including; diabetes, hypertension, heart failure anemia, and treatment measures (N-acetylcysteine use and hydration). Whereas, Mehran and colleague [10] as well as Bartholomew *et al.* [11], identified variables such as older age, chronic heart failure, diabetes, contrast volume, and anemia that were associated with increased risk of CIN. However, Dimitrios Tziakas *et al.* proposed a risk score model for contrast-induced nephropathy prediction after PCI, with good discriminating power (c-statistic 0.759) and excellent calibration (calibration slope 0.91) regarding pre-existing renal disease, metformin, history of previous PCI, peripheral arterial disease, and contrast volume ≥ 300 mL. Treatment with N-acetylcysteine seems to have no protective effect on CIN after cardiac catheterization [10, 11]. Two meta-analyses showed protective effect of NAC individually with higher doses and intravenous use [25, 26], whereas, Otavio Berwanger in a large randomized trial, found that acetylcysteine does not reduce the risk of contrast-induced nephropathy in high risk or low risk patients undergoing coronary and peripheral vascular

angiography [27].

Our study has some limitations. First, we did not assess several characteristics that affect endpoints such as previous history of CA, the number of involved vessels. Second, since we used creatinine level as indicator of renal insufficiency, the low incidence of CIN was reported than other study. While, several studies proposed cystatin C are more reliable for detecting contrast-induced nephropathy [28-31]. On the other hand, the median volume of contrast used was 100 mL, whereas majority of previous studies use greater volume of contrast media like 300 mL [4, 13, 31, 32]. Furthermore, there was no follow-up program after 24 h to assess the incidence of CIN.

In conclusion, our study showed that the most important factors affecting the incidence of CIN after CA were old age, pre-existing renal insufficiency, diuretic medication use and the volume of contrast media. According to our study the prophylactic measures did not result in a lower incidence of contrast-induced nephropathy. Hence, improving clinical decisionmaking may prevent unnecessary procedure and complication.

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