

Incidence and Predictors of Contrast Induced Nephropathy after Coronary Intervention at College of Medical Sciences Teaching Hospital, Bharatpur.

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ABSTRACT

Background and Aims: The implications of radio-contrast induced nephropathy are disastrous. In Nepal there is scarcity of data on contrast induced nephropathy. This observational descriptive study was undertaken to study the incidence of contrast induced nephropathy and to identify risk factors (predictors) for the development of contrast induced nephropathy in patients undergoing coronary angiography and angioplasty in a tertiary care hospital.

Methods: The subject consists of 540 patients undergoing coronary intervention from 2011 to 2013 were enrolled by convenient sampling technique. Two hundred ten patients were excluded from the study. Therefore, a total of 330 patients were studied and analyzed. Contrast induced nephropathy was defined as an increase of >25% or >0.5 mg/dl in pre-catheterization serum creatinine at or after 48 h after percutaneous coronary intervention. Estimated glomerular filtration rate as calculated by applying the 4 variables Modification of Diet in Renal Disease Study equation. Standard definitions were used to define the variables.

Results: Twenty seven (8.18%) patients experienced contrast induced nephropathy. The incidence of contrast induced nephropathy in patients with baseline creatinine clearance <60 ml/min was 45.9%. Contrast induced nephropathy developed in 10% of anemic and 12.5% diabetic patients.

The amount of the contrast agent administered was similar for both groups of patients (138.20±91.34ml vs. 175.56±118.86ml; $p=0.254$). No correlation was found between the amount of contrast agent administered and the change of serum creatinine concentration. Multivariate logistic regression analysis found that baseline e-GFR and baseline hemoglobin were independent predictors for Contrast induced nephropathy.

Conclusion: The overall incidence of Contrast induced nephropathy after coronary intervention in this study is high. Patients with both preexisting renal insufficiency and anemia were at high risk of Contrast induced nephropathy.

Citation

Sanjib Kumar Sharma, Laxman Dubey, Shankar Laudary, et al. Incidence and predictors of Contrast Induced Nephropathy after coronary intervention at College of Medical Sciences-Teaching Hospital, Bharatpur. Nepalese Heart Journal 2014;11(1): 3-11.

Keywords

Anemia, Coronary angiogram, Contrast induced nephropathy, Diabetes.

INTRODUCTION

Radiologic procedures utilizing intravascular iodinated contrast media injections are being widely applied for both diagnostic and therapeutic purposes. More than 1.2 million cardiac catheterization is done in the US annually.¹

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Although the incidence of contrast-induced nephropathy (CIN) is low in general population with normal kidney function, it can be much higher in those with predisposing conditions. CIN is the third leading cause of new acute kidney injury in hospitalized patients² and constitutes 11% of all hospital acquired acute kidney injury.³

CIN is generally transient and reversible form of acute kidney injury. However, it has been associated with poor clinical outcome causing considerable in-hospital morbidity and mortality, prolongs the hospital stay, and increases the incidence of chronic end-stage renal disease and the cost of health care.^{2, 4, 5, 6} Among all the procedures that uses radio contrast materials for the purpose of diagnosis and therapeutics, coronary angiography and percutaneous coronary interventions (PCI) are associated with higher risk of CIN.³

In Nepal, prevalence of cardiovascular disease and its risk factors are high.⁷ It is expected that the increasing disease burden will lead to increasing diagnostic and therapeutic cardiac interventions exposing patients to contrast media. Recognizing which of our patients are at high risk and have the potential for contrast-induced acute kidney injury is the key to improve outcomes of these patients. In this regards identification of risk factors for CIN in Nepalese population undergoing coronary angiogram/PCI will help risk stratification and help undertake preventive measures for CIN. In this background this cross sectional observational hospital based descriptive study was undertaken to study the incidence of CIN and to identify risk factors (predictors) for the development of CIN in patients undergoing catheterization in CMS-TH, Bharatpur, Nepal.

METHODS

Study Population

A total of 540 patients undergoing coronary angiogram/PCI from 2011 to 2013 were enrolled in the study by convenient sampling technique. Two hundred ten patients were excluded from the study due either due to non-availability of follow up data of serum creatinine, lost to follow up or death of the patients before completion of the study period. Therefore, a total of 330 patients who underwent elective or emergency coronary interventional procedure were enrolled. All patients received evidence based standard pre and post procedural care as per Guideline directed medical management. All patients provided written informed

consent for cardiac catheterization and PCI and for the data collection related to CIN for the study. Patients were excluded from the study if they did not provide the consent. Institutional ethical review committee approved the study.

Study Protocol

Percutaneous femoral arterial catheterization was the most widely used vascular access technique. Patients received a bolus of 2500 unfractionated heparin before the diagnostic procedure and additional 100 IU per kg body weight before the intervention, if done. The absolute amount of contrast media was recorded after each procedure. Laboratory data including pre- and post-procedural serum creatinine, glucose, serum sodium, serum potassium, and baseline hemoglobin were collected. Serum creatinine values were measured before the procedure for the baseline value and at 24 hours, 48 hours and 2 weeks. Serum creatinine was measured by Jaffe's reaction method in automatic biochemistry analyzer.

If a patient developed CIN, appropriate measure to treat either conservatively or by dialysis support was done. Decision was made in consultations with nephrologist.

Clinical Definitions

Contrast-induced nephropathy was defined as an increase of >25% or >0.5 mg/dl in pre-PCI serum creatinine at or after 48 h after PCI.^{8,9} Chronic kidney disease,⁹ hypotension,¹⁰ anemia,¹¹ myocardial infarction,¹² hypertension,¹³ cardiogenic shock,¹⁴ diabetes mellitus,¹⁵ hypercholesterolemia,¹⁶ and unstable angina¹⁷ were defined as per standard definitions.

STATISTICAL ANALYSIS

Data were entered on MS XP sheet and then was converted to SPSS PC+ 16 version for statistical analysis. Continuous variables are expressed as mean, standard deviation (SD), and categorical data were presented as absolute values and percentages. T-test and ANOVA with post sheffe test were used for parametric comparison. Mann-Whitney U and Kruskal-Wallis test were used for nonparametric comparison. Chi-square or the Fisher exact tests were used for comparison of categorical variables as required. Correlations between the amount of contrast agent administered and the change of serum creatinine concentration were evaluated with Pearson's correlation coefficient. Multivariate predictors of CIN were identified by logistic regression using stepwise selection with entry and exit criteria of $p < 0.1$. A two-sided 95% confidence interval (CI) was

constructed around the point estimate of the odds ratio (OR). The variables chosen by the model included all the potential confounding variables. All hypothesis testing was two tailed. A p value < 0.05 was considered as statistically significant.

RESULTS

The baseline clinical characteristics of study population are given in Table 1.

Table 1. Baseline characteristics of study population (n=330)

Characteristics	Male (n=222)	Female (n=108)	p value
Age (±SD)	41(±49.4)	36(±48.7)	0.655
BMI (Kg/M ²)	24.47(±3.37)	25.04(±3.39)	0.552
	<25	121	60
	>25-29.9	98	34
	>30	12	5
Systolic BP	137.69(±19.92)	138.53(±20.52) (mmHg)	
Diastolic BP	80.59(±9.87)	81.88(±12.95) (mmHg)	
Hypertension	98	55	0.213
Anemia	99	21	0.012
Acute STEMI	90	60	0.786
Acute non-STEMI	17	7	-
Unstable angina	37	11	0.715
Stable CAD	15	9	0.344
Diabetes Mellitus	45	27	0.748
Hypercholesterimia	31	26	0.179
CKD	19	8	0.074

STEMI: ST Elevation myocardial infarction,

CAD: Coronary artery disease

Out of 330 patients who underwent cardiac catheterization, 27 (8.18%) patient developed CIN after angiogram/PCI. The mean amount of contrast medium administered in the CIN group was 175.56±118.86 ml. In these patients, the mean serum-creatinine level increased from 1.36mg /dl

to 2.5mg/dl. The mean difference in serum creatinine was 1.45mg/dl. The characteristics of the patients who develop CIN were older, diabetic, had lower e-GFR and a higher incidence of anemia and baseline creatinine.

The baseline mean serum creatinine of patients without CIN and who developed CIN were 0.926±0.317 mg/dL and 1.29 ± 0.460 mg/dL respectively. Similarly e-GFR was 89.24±27.3 ml/min in patient without CIN and 62.44±25.08 ml/min patients with CIN.

There was no difference in baseline medications in patients with or without CIN. The concomitant medications administered were statin, aspirin, beta-blocker and ACE inhibitors.

Almost all patients received low molecular weight contrast media, either Iohexol or Ioversol. Few patients received iso-osmolar contrast Iodixanol (n=35). Coronary angiogram revealed that 51 (15.45%) patients had triple vessels disease. Double vessel and single vessels disease was observed in 44 (13.33%) and 106(32.12%) patients. Normal coronary angiogram was recorded in 91(28.18%). Percutaneous coronary intervention was performed in 117 (35.45%) patients.

Amount of contrast agent administered for the CIN group and the non-CIN group was similar (175.56±118.86 ml vs. 138.20±91.34 ml; p = 0.254). There was also no significant difference of proportion in diagnostic procedure, PCI and emergency cases for the CIN group and the non-CIN group.

Subgroup Analysis

Elderly Patients (≥ 70 years):

A total of 72 patients were aged 70 years and above. The incident of CIN in elderly was 12.5% and that of age below 70 years was 6.97%. The difference was statistically significant (p=0.01).

Diabetes mellitus

The incidence of CIN in diabetic patients was higher than non-diabetic population and it was statistically significant (12.5% in diabetes Vs. 6.97% in no-diabetic patients, p=0.01).

Due to relatively small number of patients in diabetes with pre-existing renal impairment size it was not possible to stratify the incidence of CIN in patients with preexisting renal dysfunction in diabetics to that diabetes without pre-existing renal dysfunction.

Preexisting impairment of renal function

The incidence of CIN in patients with preexisting impairment of renal function (baseline creatinine clearance < 60 ml/min) was 45.45% vs. 4.04% in patients with baseline creatinine clearance \geq 60 ml/min ($p < 0.001$). There was no difference regarding the amount of contrast agent administered between patients with different baseline creatinine clearance.

PCI group

The incidence of CIN was similar for the PCI and non-PCI subgroup (2.7% vs. 3.0%; $p = 0.65$). In addition, the incidence of CIN in elective cases and in emergency cases also showed no significant difference (2.9 % vs. 2.6 %; $p = 0.69$).

Anemia group

Out of 120 anemic patients, 12 (10%) patients developed CIN. The incidence of CIN in anemic patients was significantly higher than in non-anemic patients (10% vs. 7.14%; $p < 0.001$).

Multivariate Logistic Regression Analysis

Variables included in the first step of the multivariate analysis were age, sex, BMI, systolic blood pressure, diastolic blood pressure, arterial hypertension, hypercholesterolemia, LVEF, presence of coronary artery disease, presence of diabetes mellitus, STEMI, unstable angina, PCI, baseline e-GFR, amount of contrast agent administered, serum sodium, serum potassium, glucose level, hemoglobin level and ACE inhibitor medication.

Anemia was an independent predictor of CIN (OR 1.84, 95%CI 1.459 to 2.86, $p < 0.001$) when it was introduced into the multivariate model. The relative risk (RR) for the CIN after exposure of contrast agent was significant for baseline e-GFR < 60 ml/min (RR 3.68, 95% CI 2.876 to 6.392, $p < 0.001$) and anemia (RR 1.84, 95% CI 1.49 to 2.086, $p < 0.001$).

DISCUSSION

Contrast-induced nephropathy represents the third cause of in-hospital renal function deterioration.⁴ CIN is also a possible complication after coronary diagnostic and interventional procedures. In fact, renal dysfunction is a common and serious consequence following diagnostic and interventional coronary procedures. With increasing

number of diagnostic and therapeutic catheterizations each year, particularly among patients who may have serious conditions predisposing to CIN, the incidence of CIN will continuously increase. Identification of the risk factors for the development of CIN in our context may provide a window to identify risk group population for development of CIN. The ability of effective prevention of CIN in high-risk patients will provide significant public health benefits, which would potentially reduce the in-hospital mortality rate, the length of hospital stay and the subsequent use of chronic hemodialysis.

The comparison of incidence of CIN after angiography with other large studies is given in Table 2.

The incidence of CIN in patients undergoing PCI in our study was 8.18% which was much higher than the results of Rihalet al.¹⁸ The incidence of CIN in patients with impaired renal function (e-GFR <60ml/min) was higher than those with preserved renal function (45.45 % vs. 4.04%). This was consistent with previous studies, which suggested a higher incidence of CIN in patients with greater reduction in renal function.^{18, 21, 22} In a series of 7,586 patients undergoing cardiac catheterization, Rihal et al.¹⁸ found a low risk (2.4 %) of CIN in patients with normal renal function, but a high risk (30.6%) in those with serum creatinine levels \geq 3.0 mg/dl. Moore et al.²³ demonstrated a high, significant relationship between an increasing baseline level of serum creatinine and the frequency of nephrotoxicity (varying from 2% in those with baseline creatinine of < 1.5 mg/dl to 20% in those with levels of > 2.5 mg/dl). However, we had only two patients in severe renal impairment category (e-GFR <30ml/min). Both of the patients did not develop CIN. They had undergone coronary angiogram only without PCI limiting the amount of contrast exposure to minimum. Patients with severe renal insufficiency (baseline creatinine clearance < 30 ml/min) are usually expected to suffer more. CIN is associated with increased morbidity and mortality, particularly in high-risk patients who underwent percutaneous coronary interventions.^{5, 6, 18} The in-hospital mortality rate in patients developing renal insufficiency is directly related to the magnitude of the increase in the serum creatinine concentration.^{5, 24} A study by Marenzi et al demonstrates that CIN is a frequent complication after PCI in AMI even in patients with normal baseline renal function, and is associated with increased in-hospital morbidity, mortality and prolonged hospitalization.²⁵ Levey et al⁶ studied 16,248 patients who underwent radiocontrast

Table 2: Comparison of incidence of CIN after coronary angiography/PCI

Variables	Present study	Rihal et al.18	Dangas et al.19	Nikolsky et al.20
Number of patients	330	7586	7230	6773
Type of procedure	Both diagnosis and intervention	Coronary intervention	Coronary intervention	Coronary intervention
Contrast Osmolality	Low and few iso-osmolar	Low	Low	Low
Volume of contrast (ml)	156.88+105.1	292+139	285+154	273+123
Definition of CIN	Increase in creatinine of 0.5 mg/dl or 25%	Increase in creatinine of 0.5 mg/dl	Increase in creatinine of 0.5 mg/dl or 25%	Increase in creatinine of 0.5 mg/dl or 25%
Incidence of CIN	8.18%	3.3%	14.8%	13.9%
Independent predictors of CIN	Baseline CrCl (e-GFR)	Baseline serum Cr	Decreased eGFR	Estimated glomerular filtration rate
	Anemia	AMI	Periprocedural hypotension	(10 ml/min/1.73 m ² decrease)
		Shock	Higher contrast agent volumes	Baseline hematocrit
				Volume of contrast media
		Volume of contrast	Lower baseline hematocrit	(increase by 100 ml)
		Agent administered	Diabetes	Hypotension
			Pulmonary edema at presentation	Diabetes mellitus
			Intra-aortic balloon pump use	Hypertension
			LVEF<40%	LVEF<40%

procedures and found that the mortality rate in patents without renal failure was 7%, compared with 34% in those with renal failure. These data suggest that the development of CIN is highly correlated with death during the index hospitalization as well as during long-term follow-up.

CIN in elderly (>70 years) Patients

In this study, the incidence of CIN in patient's ≥ 70 years was 12.5%. The result was consistent with the finding of McCullough et al.⁵ Study by Marenzi et al. and Cigarroa et al.^{25, 26} reported ≥ 70 years of age appeared to be an independent predictor of CIN. Rich and Crecelius²⁷ reported

an incidence of CIN in patients of the same age group to be 11%. The reasons for this higher risk of CIN have not been studied but are probably multifactorial, including age-related changes in renal function, the presence of multivessel disease, and more difficult vascular access due to tortuosity and calcification of the vessels requiring relatively large amounts of contrast.

CIN in Diabetes Mellitus

Besides preexisting impairment of renal function, diabetes mellitus is another well-recognized risk factor for CIN. Clinically important CIN usually occurs in subset of

diabetics who have underlying renal insufficiency.^{10, 18} In the present study, the diabetes alone was an independent risk factor for the development of CIN. The incidence of CIN in patients with preexisting renal dysfunction was very high in both diabetic and non diabetic. As the numbers of patients were small (9 in diabetics and 20 in nondiabetic with e-GFR <60ml/min), the inference may not be valid and it is advisable to conduct a study with appropriate sample size for definite conclusion to make. Mehran et al.¹⁰ showed that in diabetics with preserved renal function and absence of other risk factors, the rate of CIN was comparable to that in a healthy population. Lautin et al.²⁸ reported that the incidence of CIN was rather low (2%) in patients with neither diabetes nor azotemia, but significantly higher (16%) in individual patients with diabetes but preserved renal function, and much higher (38%) in patients who had both diabetes and azotemia. In a large study of 1,196 patients,²⁹ the incidence of CIN associated with the administration of low-osmolar contrast medium in patients with normal renal function was 7.2% in diabetic patients and 8.5% in nondiabetics. In a study of 1,826 consecutive patients undergoing coronary intervention, McCullough et al.³⁰ concluded that diabetes mellitus is one of the strongest predictors of acute renal failure after coronary intervention. Some literatures^{5, 31} have been inconsistent with respect to diabetes as strong risk factors for CIN after PCI. Rihal et al.¹⁸ have shown in a large scale study of 7,586 patients who underwent percutaneous transluminal coronary interventions at the Mayo clinic that diabetes increases the risk of CIN in patients with baseline serum creatinine (SCr) < 2.0 mg/dl (3.7% vs. 2.0% from 0 to 1.1 mg/dl SCr, $p = 0.005$; 4.5% vs. 1.9% from 1.2 to 1.9 mg/dl SCr, $p < 0.001$), but not in patients with SCr > 2.0 mg/dl before the procedure.

CIN in Preexisting Impairment of Renal Function

Multivariate logistic regression analysis confirmed that baseline creatinine clearance was an independent risk factor for CIN in the study population. This result was consistent with other studies.^{19, 30} Rihal et al.¹⁸ used multivariate analysis; baseline serum creatinine was identified as an independent predictor of CIN. In multivariate analysis by McCullough et al.³⁰ creatinine clearance is an independent predictor of CIN requiring dialysis after coronary intervention. Renal function deterioration after exposure to contrast medium is common in patients with impaired renal function.²⁷ McCullough et al.³⁰ found that creatinine clearance of 30ml/

min or less markedly increased the incidence and severity of CIN. The renal function deterioration is an important predictor of in-hospital mortality. Dangset al.¹⁹ found CIN was one of the most powerful predictors of 1-year mortality in patients with preexisting chronic kidney disease or preserved eGFR.

CIN in Patients with Anemia

Anemia has been incorporated as risk factor for development of CIN. Our study demonstrated that presence of anemia was an independent risk factor for contrast-induced nephropathy. When anemia was introduced into the multivariate model it was an independent predictor of CIN. This finding paralleled the clinical trial finding of Nikolsky et al.²⁰ who found that lower baseline hematocrit was an independent predictor of contrast-induced nephropathy, each 3% decrease in baseline hematocrit resulted in significant increase in the odds of contrast-induced nephropathy in patients with and without chronic kidney disease. Among 7,230 consecutive patients after percutaneous coronary interventions, Dangas and colleagues²⁰ showed that decreased eGFRs and lower baseline hematocrit were most significant independent predictors of CIN in patients with chronic kidney disease.

In the present study, the incidence of CIN in patients with anemia was 10% and without anemia was 7.14%. In this patients with anemia were older than non-anemic group. This was possibly the mechanism to explain an association between anemia and higher incidence of CIN. Kim et al.³² reported that contrast media could increase oxygen affinity of hemoglobin, so oxygen delivery to the peripheral tissues might be impaired. Local renal hypoxia can be more aggravated in patients with low hemoglobin after exposure to contrast media, hence the combination of contrast-induced vasoconstriction and anemia may decrease oxygen delivery sufficiently to cause renal medullary hypoxia. Thus, it is intuitive that anemia may play a role in CIN risk. Nikolsky and colleagues²⁰ demonstrated that patients with the lowest eGFR and hematocrit had the highest rates of CIN. The threshold hematocrit at which the risk of CIN increased was < 41.2% in men and < 34.4% in women. Anemia-induced deterioration of renal ischemia and hypoxia may be one reason for the higher incidence of CIN in anemic patients.

Role of Contrast Media

There is a debate whether the quantity of contrast agent predicts the degree of renal dysfunction. Some studies

reported no relationship between the amount of contrast material and the occurrence of renal function deterioration, whereas others suggested a direct correlation.^{5, 18} Neither in the entire study population nor in any subgroup was the amount of contrast agent administered an independent predictor of CIN in the present study. The amount of the contrast agent was similar for CIN and non-CIN patients. No correlation was observed between the amount of contrast agent administered and the change of serum creatinine concentration. In patients with different baseline creatinine clearance, the amount of contrast agent administered in CIN patients did not show any difference when compared to non-CIN patients. However, due to limited sample size in subgroup population in present study, it may not be appropriate to definitely conclude that the amount of contrast was not associated with development of CIN in the subgroup of patients. Study with larger population sample is advisable in this regard. There is a general consensus on the use of small dose of contrast agent, and that the avoidance of repetitive, closely spaced studies represents one of the most important recommendations to prevent CIN.³³ McCullough et al.³⁴ found that 100 ml contrast medium was the cutoff dose below which there was no CIN requiring dialysis undergoing coronary angiography. Briguociet al.³⁵ identified a volume of 140 ml as the best cutoff value for predicting the occurrence of CIN. These data emphasize the necessity for limiting the amount of contrast dye

administered when dealing with patients with impaired renal function.

This study has certain limitations. The sample size in the study is relatively small. However, certain risk factors could still be identified in this study. The significant loss to follow up might also have led to sample selection bias leading inappropriate incidence of CIN.

Because the follow-up assessment time of renal function in our study was at pre-specified, therefore, we might have missed a later (after 48 hours) increase in serum creatinine. This might have resulted in a slight underestimation of CIN.

We calculated e-GFR on the basis of 4 variables MDRD equation. This equation though well validated in western population, the performance of the equation in Nepalese population is not known. This might have influenced the categorization of grading of renal function.

CONCLUSIONS

The overall incidence of CIN after cardiac catheterization/PCI exposure in study populations is high using guideline-based recommendations for prophylaxis of CIN. Patients with both preexisting renal insufficiency and anemia significantly increase the incidence of CIN. Similarly, elderly populations are at increased risk of developing CIN.

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