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CONTRAST-INDUCED ACUTE KIDNEY INJURY: THE SIN OF PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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Contribution

MKB, conceived the idea. JAS & RKplanned the study. TS & MK did the data collection. NHR & NQ drafted the manuscript. All the author contributed significantly in manuscript submission.

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ABSTRACT

Objective: To determine frequency of contrast-induced nephropathy (CIN), and post procedure complications in-hospital mortality in patients after undergoing Primary Percutaneous Coronary Intervention for acute ST-Elevation Myocardial Infarction (STEMI).

Methodology: This cross sectional study includes patients, who underwent primary percutaneous coronary intervention at NICVD Karachi from 8th October 2016 to 7th April 2017. Rise of at least 0.5 mg/dL in serum creatinine level or a 25% increase from baseline within forty-eight to seventy-two hours after contrast administration was used as criteria for contrast induced nephropathy. Demographic characteristics, clinical history, presentation, post procedural complications, and in-hospital mortality in CIN and non-CIN group were assessed and compared.

Results: Of 282 patients 69.86% (197) were males with mean age of 54.77 ± 11.18 years. Contrast-induced nephropathy was observed in 12.41% (35) patients. Proportion of female patients was significantly higher in CIN group. Diabetes, hypertension and CKD remain the major risk factors. Amount of contrast used, serum creatinine, length of hospital stay, and mortality were significantly higher in CIN group. After the adjustments for potential effect modifiers the only statistically significant factors were found to be female gender and contrast used ⩾ 200ml (p= 0.012 and 0.01 respectively).

Conclusion: CIN after primary PCI is strongly and positively associated with female gender, hypertension, chronic kidney disease, diabetes mellitus, presence of shock and more than 200 ml of contrast use.

Key Words: Contrast induced nephropathy, Primary PCI, ST-segment elevation myocardial infarction.

INTRODUCTION

Declinein kidney functions is fairly common in the field of interventional cardiology. Such alterations in kidney function are often seen with the utilization of contrast, hence called contrast induced acute kidney injury (CI-AKI), also known as contrast induced nephropathy. Contrast induced nephropathy (CIN) is associated with increased morbidity and mortality prolonged hospitalization, and increased healthcare cost. It is the third most common cause of hospital acquired renal failure, after decreased renal perfusion and use of nephrotoxic medications. The incidence of contrast induced nephropathy as a post procedure complication of radiographic diagnostic and intervention varies markedly in past studies. The incidence rate is varying from one study to other depends on the definition used, with regard to number and type of risk factors and length of patients follow-up. The incidence rate reported in literature is 3-22%.[1-4]The reported incidence from the National Cardiovascular Data Registry (NCDR) was 7% in general population and 16% in those presenting with acute myocardial infarction (MI).[5]

Acute kidney injury after cardiac catheterization is related to the use of intravascular contrast agents. However, in spite of their widespread use in radiographic diagnostic and intervention studies, the mechanism of kidney injury caused by contrast agents has not been fully elaborated.[6]There are different studies which devise the pathophysiological mechanisms of direct toxic injury to the renal tubules and ischemic injury to the renal medulla, from vasomotor changes and decreased perfusion. The later appears to be mediated impart by the development of reactive oxygen species, such as superoxide, and has important implications for treatment with scavenging agents.[7]

Chronic kidney disease, diabetes, medications and hemodynamic changes,etc are causative factors that can exaggerate the development of acute kidney injury (AKI) after cardiac catheterization. Volume depletion and hemodynamic alterations from heart failure or cardiogenic shock may exacerbate contrast induced nephropathy (CIN) by decreasing renal perfusion and predisposing the renal medulla to ischemic injury.[8,9]Such a pathophysiological state becomes even more complicated and oblique in patients undergoing primary percutaneous coronary intervention (PCI) because of high thrombogenic state, a high burden of inflammation due to the myocardial damage, and a potential decrease in perfusion to the kidneys through vasoconstriction or hemodynamic instability.

The interventional cardiology and radiology literature has traditionally defined contrast induced acute kidney injury as a rise in serum creatinine level of at least 0.5 mg/dL or a twenty-five percent from baseline within forty-eight to seventy-two hours after contrast administration.[8]

Apart from the use of serum creatinine level and calculation of the glomerular filtration rate, a simple risk score can quantify the risk of CIN prior to the diagnostic and therapeutic radiographic procedures. An ideal risk model, however, would allow clinicians to prospectively identify patients at high risk for CI-AKI before cardiac catheterization such as Mehran et al.Gurm HS et al,used a cohort of 68,573 PCI procedures in Michigan to develop an easy-to-use risk prediction algorithm that utilizes only pre-procedural variables to accurately estimate a patient's risk of CI-AKI and a new requirement for dialysis.[3] CIN of $<1\%$ are considered low risk, those with 1-7% are considered at intermediate risk and those with an estimated risk $> 7\%$ are classified as high risk.[10]

The purpose of this study was to determine frequency of contrast induced nephropathy (CIN), post procedure complications, and in-hospital mortality in patients presenting with acute ST-Elevation Myocardial Infarction (STEMI) undergoing primary percutaneous coronary intervention at a tertiary care hospital Karachi, Pakistan.

METHODOLOGY

This cross sectional study was conducted at catheterization laboratory of National Institute of Cardiovascular Disease (NICVD) Karachi, Pakistan. In this study, we summed up all consecutive patients presented with acute ST-Elevation Myocardial Infarction (STEMI) who were treated with primary PCI during the study period of 8th October 2016 to 7thApril 2017.Sample size for this study was calculated using WHO sample size calculator version 2.0, taken confidence level of 95%, margin of error of 3.0%, and anticipated population proportion of 7%. Additional 15 patients were recruited in account for any potential information loss and 11 patients with missing data were excluded from the analysis of data.[5]

Data was collected after approval of institutional ethical review committee and informed consent was taken by principal investigator from all enrolled patients. Data was collected on predefined structural questionnaire. Demographic characteristics and clinical history of the patients was taken regarding hypertension, diabetes, dyslipidemia, smoking, family history, coronary artery disease (CAD) and chronic kidney disease (CKD). Presenting symptomatology of the patient; chest pain, shortness of breath, state of shock, and survival of sudden cardiac arrest were recorded. Primary PCI was performed in all patients as per the institutional practice guidelines of the procedure and amount of contrast (ml) used during the procedure was recorded. Serum creatinine (mg/dL) level was measured pre-procedure and 48 to 72 hours post procedure. In-hospital outcome, duration of stay (days) and post procedure complications were recorded. Rise of more than or equal to 0.5 mg/dL in serum creatinine or an increase

of 25%in serum creatinine within 48 to 72 hours after contrast administration is used as criteria for contrast induced nephropathy (CIN).

Statistical package for social sciences (SPSS 21) was used to analyze the data. Mean ± SD was calculated for quantitative variables and frequency and percentages for categorical variables. Kolmogorov–Smirnov (KS) test was applied to check the normality of the continuous variables and appropriate Mann-Whitney U test or Student's t-test was applied to compare the continuous variables between CIN and non CIN group. Fisher's Exact test or Chi-square test was applied to assess the association between CIN and post procedure complications and in-hospital outcomes. Odds Ratio of CIN with 95% confidence interval was calculated by potential risk factors. Multivariate logistic regression was performed taken CIN as dependent variable and all the significant factors from univariate analysis as independent variables. Two-sided $p \leqslant 0.05$ was taken as criteria for statistical significance.

RESULTS

Out of 282 patients 69.9% (197) were males, mean age of the patients was 54.77 ± 11.18 years and 62.1% (175) patients were more than 50 years of age. Diabetes mellitus was present in 33.0% (93) patients, hypertension in 58.5% (165), smoking in 30.5% (86), dyslipidemia in 26.6% (75), positive family history in 6.4% (18), and chronic kidney disease was observed in 3.5% (10) of the patients.

Presentation to the hospital with chest pain was observed in 83.3% (235) patients, chest pain along with shortness of breath (SOB) was observed in 7.4%(21) patients, 2.1%(6) patients survived sudden cardiac arrest, and 7.1% (20) patients presented in state of shock. Majority, 78.7% (222), of the patients were presented in Killip class I, 6.7% (19) in class II, 7.4% (21) in class III, and 7.1% (20) patients were presented in Killipclass IV.

Contrast induced nephropathy (CIN) was observed in 12.4% (35) patients.Overall mean amount of contrast used was 164.66±31.92 ml, and rise in mean level ofserum creatinine within 48 to 72 hours of contrast exposure was 0.07±0.29mg/dL.

For 78.0% (220) patients had no post procedure complications and complications were relatively higher in CIN group. Significantly higher number of patients in CIN groups needed ventilator support and Thrombolysis in Myocardial Infarction (TIMI) major bleeding. ($p = 0.035$ and 0.042 respectively). In-hospital mortality was 6.1% in non CIN group while it was significantly higher in CIN group (25.7%) with ($p < 0.001$).In-hospital mortality, amount of contrast used, and length of hospital stay were significantly higher in patients with CIN. Post procedural complicationsand in-hospital outcome are summarized in Table 1.

Univariate analysis showed thatCIN has significant association with female gender, presence of shock, diabetes mellitus, hypertension, CKD and more than 200 ml of

Table 1: Post Procedure Complications and in-Hospital Outcome by Overall and Comparison of CIN and non CIN Group (n=282)

Variables	Total	Contrast Induced Nephropathy (CIN)		
	(n = 282)	No (n=247)	Yes (35)	P-value
Amount of contrast used (ml)	164.66 ± 31.92	162.77 ± 32.07	178 ± 27.76	0.007*
Length of Stay (days)	3.09 ± 1.41	2.97 ± 1.16	3.91 ± 2.42	0.025*
Complications				
No Complications	220 [78.0%]	197 [79.8%]	23 [65.7%]	0.053
Dissection	6 [2.13%]	5 [2.0%]	1 [2.9%]	0.552
Slow/No flow	14 [4.96%]	10 [4.0%]	4 [11.4%]	0.08
Shock	7 [2.48%]	6 [2.4%]	1 [2.9%]	0.609
Pulmonary Edema	11 [3.9%]	11 [4.5%]	0 [0%]	0.226
Need of intraaortic balloon pump (IABP)	3 [1.06%]	3 [1.2%]	0 [0%]	0.671
Need of Ventilator	11 [3.9%]	7 [2.8%]	4 [11.4%]	0.035*
Heart Block	10 [3.5%]	8 [3.2%]	2 [5.7%]	0.358
Thrombolysis in Myocardial Infarction (TIMI)Major Bleeding	3 [1.1%]	1 [0.4%]	2 [5.7%]	0.042*
In hospital outcome				
Mortality	24 [8.5%]	15 [6.1%]	9 [25.7%]	<0.001*

*Statistically significant at 5% level of significance
**P-values are based on Fisher's Exact test for categorical variables and Mann-Whitney U test for continuous variables
^ Multiple complications, other than CIN, were observed in three patients

contrast used. While other potential predictors such as multi vessel disease, smoking, dyslipidemia, and positive family history had no statistically significant association with CIN with p-values of 0.15, 0.23, 0.0.54, and 0.39 respectively. Occurrence and risk assessment of CIN by patient characteristics are summarized in Table 2.

Hosmer and Lemeshow Test Chi-square value for multivariate logistic regression was 5.76 with p-value of 0.45 (>0.05) at degrees of freedom of 6. The only statistically significant factors were female gender and contrast used ⩾ 200ml with p-values of 0.012 and 0.01 respectively. Multivariate logistic regression analysis of CIN is presented in Table 3.

Table 2: Occurrence and Risk Assessment of Contrast Induced Nephropathy (CIN) by Patient Characteristics (n=282)

	Base	CIN	Odds Ratio (OR)		**p-value
	N	n [%]	OR	95% CI	
Gender					
Female	85	20 [23.5%]	3.73	1.8 - 7.72	<0.001*
Male	197	15 [7.6%]			
Diabetes Mellitus					
Diabetic	93	20 [21.5%]	3.18	1.54 - 6.55	0.001*
Non-diabetic	189	15 [7.9%]			
Hypertension					
Hypertensive	165	29 [17.6%]	3.94	1.58 - 9.84	<0.001*
Non hypertensive	117	6 [5.1%]			
Smoking					
Smokers	86	13 [15.1%]	1.41	0.67 - 2.95	0.23
Non smokers	196	22 [11.2%]			
Dyslipidemia					
Yes	75	9 [12.0%]	0.95	0.42 - 2.13	0.54
No	207	26 [12.6%]			
Family History of CHD					
Yes	18	3 [16.7%]	1.45	0.4 - 5.29	0.39
No	264	32 [12.1%]			
Chronic Kidney Disease					
Yes	10	5 [50.0%]	8.07	2.21 - 29.49	0.004*
No	272	30 [11.0%]			
Contrast used					
= 200ml	51	13 [25.5%]	3.25	1.51 - 7.0	<0.001*
< 200ml	231	22 [9.5%]			
Presence of shock					
Yes	20	6 [30%]	3.44	1.23 - 9.66	0.03*
No	262	29 [11.1%]			
Number of vessels involved					
Multi vessels	183	26 [14.2%]	1.66	0.74 - 3.69	0.15
Single vessel	99	9 [9.1%]			

*Statistically significant at 5% level of significance
**P-values are based on Fisher's Exact test
CI = Confidence interval

Table 3 : Multivariate Logistic Regression Analysis of Contrast Induced Nephropathy (CIN) (n=282)

Factors	OR	95% CI	p -value
Female [yes]	2.88	1.26 - 6.57	0.012*
Presence of shock [yes]	1.82	0.53 - 6.24	0.338
Contrast used = 200ml [yes]	3.17	1.33 - 7.57	0.01*
Diabetes Mellitus [yes]	1.76	0.79 - 3.94	0.169
Hypertension [yes]	2.52	0.97 - 6.59	0.059
Chronic Kidney Disease [yes]	3.86	0.88 - 17.05	0.075
Constant	0.02	-	<0.001*

Dependent variable = Contrast Induced Nephropathy[yes]
CI = Confidence interval
*Statistically significant at 5% level of significance

DISCUSSION

Contrast induced nephropathy (CIN) in patients withacute STEMI, undergoing primary percutaneous coronary intervention (PCI) is associated with increased risk of post procedural complications and outcomes, such as prolonged hospitalization and in-hospital mortality. This study is an attemptto determine prevalence, contributing risk factors and in-hospital outcome of CIN. In our study 12.4% (35) patients develop CIN. Although, in studies with similar study subjects, CIN found in 7-19%.[5]And results of these studies are paralleled with results of our study. Insights from the NCDR Cath-PCI Registry by Tsai TT et al. reported, in cohort of 985,737 patients AKI was present in7.1% (69,658) patients.[5]

Narula A et al. studied 2,968 subjects and Contrast-induced acute kidney injury occurred in 16.1% (479) patients.[11] Marenzi G et al. studied 208 AMI patients and CIN occurred in 19.23% (40) patients.[1]Mehran R et al. studied 8,357 patients and CIN occurred in 13.3% (1,115) patients.[3]Ullah I et al. studied 177 patients undergoing PCI and CIN was reported in 10.2% (18) patients.[12] Similarly, Lucreziotti S et al. studied 323patients undergoing primary PCI and CIN was detected in 15.2% (49) subjects.[13]

The results of our study with reference to contributing risk factors are similar to earlier published literature; in our study significant association of CIN is observed with female gender, hypertension (HTN), chronic kidney disease (CKD), diabetes mellitus (DM), presence of shock and high amount of contrast use (⩾ 200 ml).Insights from the NCDR Cath-PCI Registry by Tsai TT et al. reported high prevalence of comorbidities including hypertension, diabetes, and dyslipidemia. Study further elucidates, patients are more likely to have had a congestive heart failure, history of anemia, CKD and acute coronary syndromes.[5]Moreover, study conducted by Lucreziotti S et al. reported significant association of CIN with female gender and impaired renal function (CKD).[13]

The results of our study with reference to post procedural complications and adverse clinical endpoints of prolonged hospital stay (3.91 ± 2.42 days vs. 2.97 ± 1.16 days), need of ventilator (11.4% vs.2.8%), death(25.7% vs. 6.1%)and TIMI major bleeding (5.7% vs. 0.4%) were significantly higher in patients who developed CIN.Insights from the NCDR Cath-PCI Registry by Tsai TT et al. reported, of the 69,658 patients in whom AKI developed after PCI, the in-hospital rates of MI,bleeding, and death was 3.8%, 6.4%, and 9.6% respectively, compared with 2.1%, 1.4%, and 0.5%, respectively, in patients in whom AKI did not develop.[5] In study conducted by Lucreziotti S et al. found significantly higher in-hospital mortality in patients developing CIN than in patients without CIN (20.4% vs. 2.6%) with p<0.001.[13]

Since development of contrast induced nephropathy (CIN) in subjects undergoing primary PCI is well established fact, it is logical to adopt preventive strategies in patients at higher risk of CIN. In our study six simple variables such as female gender, DM, HTN, CKD, presence of shock and use of high amount of contrast (⩾ 200 ml) are found to be highly associated with CIN.In our study, we found odds ratio of 3.73, 3.18, 3.94, and 3.44 for female gender, DM, HTN, and presence of shock respectively. Furthermore, our analysis demonstrates that odds ratio of CIN is 8.07 times in patients with baseline CKD. Regardless of the underlying mechanism, an increase in creatinine concentration at baseline during the acute phase of STEMI may represent a surrogate marker for more severe and extensive atherosclerosis, major adverse cardiovascular events and circulatory instability.[14]

Upon multivariate analysis, even after adjusting for the potential effect modifiers, female gender and amount of contrast used for the procedure remained the significant

factors associated with CIN. And the primary modifiable risk factor is the amount of contrast used during the procedure. Many studies have documented a similar strong positive relationship between amount of contrast and occurrence of CIN.[1,15,16] Hence our evidence supports that the contrast induced acute kidney injury is one of the sins of Primary Percutaneous Coronary Intervention.

Although, more complex coronary interventions invariably used higher volumes per procedure.[17] In our study significantly higher amount of contrast used is observed in patients who developed CIN (178 ± 27.76 vs. 162.77 ± 32.07) with p-value of 0.007. In study conducted by Marenzi G et al. demonstrated a significant rise in incidence of CIN with increase of volume of contrast and significantly higher amount of contrast in patients who developed CIN (378 ± 200 vs. 286 ± 125) with p-value of 0.008.[1]

Potential preemptive strategy to minimize the CIN is to optimize volume status of the patient and infuse normal saline hence monitoring adequate hydrations before and after the procedure according to recommended doses, and the amount of contrast used for the procedure in high risk patients. Though various pharmacologic and non-pharmacologic agents are suggested for prevention but data is still oblique andunclear and demands further studies in this regards. Despite the varying degree of agreement among the studies on various contrast agents, nonionic low-osmolar or iso-osmolarcontrast media is the preferred choice among the different practitioners.[17,18]

LIMITATION

Our study has some limitations. First and foremost important limitation is population of our study is confined to single center study with less diversified patients flow. Second, the criteria of CIN was based on the absolute or relative rise in serum creatinine level within 48 to 72 hours, compared with baseline level, after contrast exposure and other alternative explanations for renal impairment have been excluded. Study sample comprises of high risk patients with AMI and advanced age, post procedure outcome and complications can be higher than other studies which might enroll low risk subset of population.

CONCLUSION

Development of contrast induced nephropathy after primary PCI is associated with female gender, diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), presence of shock and higher amount of contrast use.It resulted in increased post procedural complications, adverse clinical endpoints such as, prolonged hospital stay, need of ventilator, death, TIMI major bleeding, and of course increase health care cost.

It is recommended that patients at higher risk of CIN should be identified and targeted preventive strategies should be adopted preemptively to negate such a possible occurrence of devastating pathophysiological state which often results in major cardiovascular events.

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