VOLUME - 9, ISSUE - 7, JULY - 2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Cardiology

Contrast Induced Nephropathy In Patients Undergoing Coronary Interventions (ongoing study)

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ABSTRACT

Background: One of the important cause of hospital-acquired acute kidney injury is Contrast induced nephropathy and it affects between 2% of the general population to 50% of high-risk subgroups following coronary intervention.

Objectives: To evaluate the incidence of contrast induced nephropathy (CIN), and to study the association of various risk factors with CIN in our population.

Methodology: A total of 500 patients (348 males and 152 females) who received nonionic iso-osmolar contrast media during percutaneous coronary intervention (PCI) were enrolled in our study. CIN was defined as a relative increase of 25% or an absolute increase of >0.5 mg/dl in serum creatinine levels two days post procedure.

Results: The overall incidence of CIN in our study was 18.8% .In univariate analysis: age >75 years, hypotension, diabeties mellitus, heart failure, CKD [creatinine >1.5mg/dl] and increased contrast volume associated with a trend towards risk of CIN whereas gender and anemia failed to show any statistically significant association with CIN. As Mehran's risk score (MRS) or number of associated risk factors and volume of contrast used increases, the incidence of CIN increases. The incidence of CIN in our study for low, intermediate, high and very high risk groups based on MRS was 17.76%, 13.89%, 30.61% and 41.17% respectively.

Conclusion: CIN has association with many risk factors, in our study we found that whenever multiple risk factors or MRS >10 are present in an individual patient, lowest dose of contrast should be used by using "maximal allowable contrast (MAC) dose" to prevent the occurrence of CIN.

KEYWORDS : Contrast-induced nephropathy, Non ionic iso-osmolar contrast media, Mehran's risk score, percutaneous coronary intervention.

INTRODUCTION

In past few years the use of intravascular iodinated contrast agents has continued to increase. Contrast induced nephropathy [CIN] is an iatrogenic renal injury that occurs due to use of radio-opaque contrast media. CIN is recognised as the third most common cause of hospital acquired acute kidney injury (AKI), while nephrotoxic medications and renal hypoperfusion are the two common causes of CIN. CIN accounts for 11% to 12% of all cases of in hospital AKI with in hospital mortality rate of 6% [1,2,3]. A small rises in serum creatinine have been demonstrated to occur in 8 to 35% of patients admitted to hospital without exposure to contrast media so it is very important to exclude other causes for AKI [4]. Coronary interventions are associated with the highest rates of CIN among all procedures utilizing contrast media for diagnostic or therapeutic purposes, [2]. In majority of cases, CIN usually resolved spontaneously As after exposure to contrast media serum creatinine usually rises in 3 to 5 days and returns to baseline within 1–3 weeks [5,6]. Indian patients have higher overall incidence of CIN (18.8%) compared to 13.1% incidence in western population (MRS formulated in western population)[7]. This high incidence of CIN in Indian patients is because of higher atherogenic burden as well as higher incidence of risk factors for CIN.

CIN: AKI secondary to contrast media use can occur from many causes including atheroembolism, ischemia or nephrotoxicity action of the contrast itself. The latter is referred to as CIN. The most widely used definition for CIN is that of the European Society of Urogenital Radiology (ESUR) which defines CIN as "an increase in serum creatinine by >25% or an absolute increase of 44.2 mmol/l [0.5 mg/dl] within 3 days after intravascular administration of contrast medium, without an alternative etiology" [8]. Before diagnosing CIN it is important to rule out other causes of AKI (prerenal /intrinsic /post renal).

Risk prediction scores for CIN: Various risk scores are available for the prediction of CIN in patients undergoing interventions with radio- contrast media [9, 10]. ACEF score is one of the simple risk scoring system for predicting CIN. It is based on three variables namely age, creatinine level and ejection fraction and has been developed for patients undergoing coronary angiography [11, 12]. Another scoring system by Mehran et al has been widely used in western populations (not in India) and is provided with an online calculator. The only drawback with the MRS is that it can only be calculated after the completion of procedure.

MATERIAL AND METHODS

This is an ongoing prospective observational study to evaluate various risk factors associated with the incidence of CIN in post PCI patients. A total 500 coronary artery disease (CAD) patients were enrolled (age ≥ 18 years) and admitted to undergo PCI, 250 patients were enrolled between January 2017 to december 2018 and another 250 patients were enrolled between January 2019 to December 2019 at a tertiary care hospital in north India. Clinical history taken and blood samples were obtained at admission and at 48 hours after the cornonary procedures both diagnostic and or therapeutic. Nephrotoxic drugs stopped 24 hours before the procedure. The sole contrast medium used in our study was a nonionic, iso osmolar contrast medium (iohexol). Following the procedure, serum creatinine levels were obtained from the same reference laboratory where preprocedure serum creatinine levels were determined to avoid the inter laboratory variability in the measurements of serum creatinine levels. Pre and Post

procedure serum creatinine levels were compared to determine the CIN. CIN diagnosed in our study as a 25% relative increase, or a 0.5 mg/dl (44μmol/L) absolute increase in serum creatinine after 48 hours of contrast exposure, in the absence of an alternative cause. We evaluated the incidence of CIN, need for dialysis and CIN related mortality during index hospitalisation and the Mehran's risk score used to predict the incidence of CIN in patients belonging to the respective risk groups. Following exclusion criteria was used: (a) Allergic reaction to contrast agents or iodine, (b) Patients with single functional kidney, (c) Serum creatinine >2mg/dl, (d) Patients on hemodialysis regimen, (e) Pregnancy, (f) Patient with pre and post procedure serum creatinine level analysis done from different laboratory, (g) active malignancy. Data of all patients collected and entered in Microsoft excel and analysed by using SPSS16 version. P value <0.5 considered statistically significant.

Mehran's risk score calculation

Risk factor	Risk score
Hypotension	5
IABP	5
CHF	5
Age>75 yrs	4
Anemia	3
Diabetes	3
Contrast media volume	1 for each 100cc^3
Serum Cr >1.5 mg/dl Or eGFR (ml/min/1.73m^2)	4 Or 2 for 40-60 4 for 20-40 6 for <20

Total risk score	Risk of CIN	Risk of dialysis
<5	7.5%	0.04%
6-10	14%	0.12%
11-16	26.1%	1.09%
>16	57.3%	12.6%

RESULTS

All 500 patients enrolled in this study were adults with age ranging from 18 to 85 years. CIN occurred in 94 (18.8%) patients. The different risk factors evaluated in our study were age, gender, hypotension, diabetes mellitus (DM), volume of contrast agent, congestive heart failure, anemia and preprocedural serum creatinine levels. There was a male predominance observed in our study, with 348 (69.6%) were males and 152 (30.4%) were females. Table 1 showing univariate analysis of binary logistic regression for the dependent variables. Risk factors such as age >75 years, CHF, hypotension, DM, CKD creatinine>1.5mg/dl] and increased contrast volume have shown statistically significant association (p<0.05) with risk of having CIN and no significant association was seen for gender and anemia with CIN.

In our study, 304 patients (60.8%) had low MRS i.e. less than five; 130 patients (26%) had MRS of 6-10; 49 patients (9.8%) had high MRS (11-16); and 17 patients (3.4%) had very high MRS (>16). The incidence of CIN in our study was 17.76%, 13.89%, 30.61% and 41.17% among patients having low, intermediate, high, and very high Mehran's risk score (based on MRS) respectively. The risk of CIN and need for dialysis increased with the increase in number of associated risk factors. Dialysis was required in 4% of patients having high MRS and in 17.64% patients having very high Mehran's risk score [p < 0.022]. Among patients who developed CIN post procedure, five patients required hemodialysis (5.31%) and one patient died of sudden cardiac arrest in hospital (Table 2).

Table1. Baseline parameters and comparison between patients with and without CIN

Risk factors		Patients (%)	CIN (%)	Relative Risk	P value
Age > 75 yrs	Yes	60 (12%)	25 (41.6%)	2.6	<0.001
	No	440 (88%)	69 (15.6%)		
Gender	Male	348 (69.6%)	67 (19.3%)	1.08	0.69
	Female	152 (30.4%)	27 (17.7%)		
Creatinine >1.5 mg/dl	Yes	27 (5.4%)	15 (55.55%)	6.23	<0.001
	No	473 (94.6%)	79 (16.7%)		
CHF	Yes	46 (9.3%)	35 (76.08%)	5.85	<0.001
	No	454 (90.7%)	59 (12.9%)		
Hypotension	Yes	36 (7.2%)	22 (61.1%)	3.92	<0.001
	No	464 (92.8%)	72 (15.5%)		
Anemia	Yes	80 (16%)	16 (37.5%)	1.07	0.764
	No	420 (84%)	78 (18.57%)		
Diabetes	Yes	141 (28.2%)	52 (36.88%)	3.15	<0.001
	No	359 (71.8%)	42 (11.69%)		
IABP	Yes	2*	1 (50%)	0.319	0.188

*In current study IABP was used in only 2 patients out of total 250 patients who were enrolled during 2017-18. IABP was not used in another 250 patients who were enrolled in 2019. One patients developed CIN out of those two patients (P = 0.188).

Table2: The split up of the patients based on the MRS.

Mehran's risk score	Risk category	Patient %	CIN %	p value	Dialysis in our study	p value
≤ 5	Low	304 (60.8%)	54 (17.76%)	0.459	0%	---
6-10	Intermediate	130 (26%)	18 (13.89%)	0.093	0%	---
11-16	High	49 (9.8%)	15 (30.61%)	0.032	2	0.022
>16	Very high	17 (3.4%)	7 (41.17%)	0.016	3	<0.001

An exponential increment seen in CIN incidence with increase in volume of contrast agent (table3). A significant higher incidence of CIN was seen in patients in whom > 100 ml contrast agent was used [p<0.001]. Table 3

Table- 3 showing relation between contrast volume and development of CIN.

Contrast (ml)	Total patients	Patients without CIN	Patients with CIN
≤ 100	175	161	12 (6.85%)
101-200	296	231	67 (22.63%)
201-300	29	14	15 (51.72%)

DISCUSSION

The incidence of CIN varies widely. The overall incidence of CIN in our study was 18.8%. The higher incidence of CIN in our study was due to presence of multiple risk factors and complex PCI including CTOs interventions. In our study, we used a CIN risk stratification score based on eight readily available variables as used in Mehran's risk score calculation, and we observed that an exponential increment occurs in CIN risk with increase in number of these risk factors. The two larger studies of 7586 and 8628 patients undergoing PCI reported incidences of CIN of 3.3% and 16.5%, respectively [13, 14]. Dr. K. Sreekanth et al reported the incidence of CIN as high as 28% among the population undergoing cardiac catheterization [15].

The MRS categorizes patients into 4 risk categories. The MRS offers not just the risk of CIN but also outlines the risk of hemodialysis specific to each category [7]. Figure 1 showing comparison of incidence of CIN in our study and Mehran's study. When the patients were subclassified based on the Mehran risk score {MRS} it was seen that 54 patient [17.76%] with an MRS <5 developed CIN. In our study the incidence of CIN in the high and very high risk groups with MRS of >10 was higher (p = 0.032) compared to the patients with MRS of <10. The observed incidence of CIN in patients having low and high risk score was higher than the expected risk based on the

MRS. The incidence of CIN in patients having MRS of >6-10, was similar in our study and in Mehran's study. While the incidence of CIN in very high risk group in our study is low compared to Mehran's very high risk group (Fig 1). In our study, higher incidence of CIN was seen in patients having MRS of <5 compared to patients with MRS of 6-10. The reasons behind this high incidence of CIN in low risk group (MRS<5) patients of our study were (1). High contrast volume (>200 ml) was used, as complex PCI was done in these patients, (2). Some patients were having reduced eGFR or raised Sr. creatinine and in them high contrast agent volume had to be used secondary to procedure related complications, (4). Due to more number of elderly or diabetic patients in low risk group.

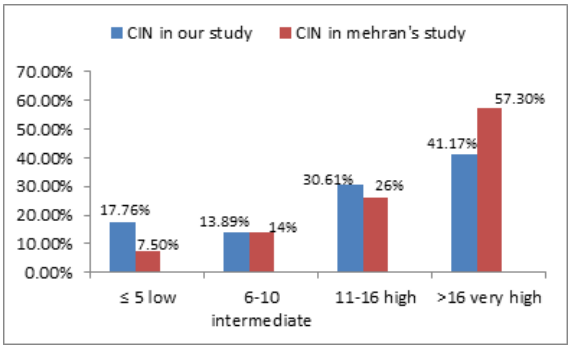

Fig 1 Figure showing comparison of CIN in our study versus risk of CIN based on MRS.

Advanced age is a non modifiable risk factor for the occurrence of CIN [16]. Ageing predispose patients to renal salt and water wasting due to reduction in renal mass, function, and perfusion. In a study by Mehran et al in 2004 [12] the incidence of CIN in patients of age >75 years was as high as 21.8% [17]. The incidence of CIN in the elderly patients was higher than younger patients in our study (41.6% vs. 15.6%); (P < 0.001).

In one study female sex was found to be an independent predictor of CIN [17], while in another study male gender was an independent risk factor for CIN [5]. However, in our study, no statistically significant gender preponderance was seen [P= 0.69].

Heart failure is associated with increased risk of CIN. In the studies done by Rihal et al [19] and Bartholomew et al [20] CHF is an independent risk factor for CIN. Our study also shown significantly higher incidence of CIN (76.08%) in heart failure patients [P < 0.001].

Preexisting renal insufficiency is one of the major risk factor for CIN. The incidence of CIN in patients with underlying chronic kidney disease is extremely high, ranging from 14.8 to 55% [18, 19]. In our study, CIN occurred in 55.55% patients with creatinine >1.5mg/dl and the baseline serum creatinine levels of those who developed CIN were higher than those who did not develop CIN (P<0.001) Out of total 94 patients who developed CIN in our study, only 2 patients in high risk group (MRS = 11-16) and 3 patients in very high risk group (MRS >16) required hemodialysis. One patient died of sudden cardiac arrest in hospital from these 5 patients who underwent hemodialysis. Although, it is difficult to establish that CIN was actually the cause of the death in that patient, however, CIN is a marker for increased mortality.

No significant association was seen between anemia and CIN [p=0.764], possibly because of only mild anemia (mean Hb 11.44 mg/dl), adequate hydration and avoidance of nephrotoxic drugs. However in various studies it was found that a baseline hematocrit value < 39% for men and < 36% for women is a risk for developing CIN [21]. With every 3% decrease in the haematocrit the odds of CIN in patients with CKD is significantly increased [22].

It is seen that nitric oxide dependent renal vasodilation is characteristically altered in Diabetes mellitus patients, and the renal outer medullary pO2 is significantly reduced [23]. DM was seen to increase the risk of CIN only if there was pre-existing diabetic microangiopathy [24]. The incidence of CIN in diabetic patients varies from 5.7 to 29.4% [25]. In our study incidence of CIN in DM was 36.88% [p < 0.001].

The volume of contrast is a modifiable risk factor in the development of CIN [7]. Our study shown that as volume of contrast agent increases, an exponential increment seen in CIN incidence (P < 0.001) (table 3). Low dose of contrast agent defined as <30-125ml or <5ml/kg, is less nephrotoxic and associated with lower risk of CIN. Brown et al proposed formula for "maximal allowable contrast (MAC) dose" {contrast volume limit in ml = [5 × body weight in kg]/ [88.4 × SCr (mol/l)]}, which correlated, with incidence of CIN [26]. Various studies shown a positive correlation between volume of contrast injected and risk of occurrence of CIN [27, 28].

IABP insertion may be linked with CIN through mechanisms that may either provoke or potentate renal impairment via (a) atheroemboli to the renal circulation (b) as a partial occlusion of the renal blood flow if it is positioned too low (i.e. in the abdominal instead of the descending thoracic aorta. Hypotension during or after PCI and use of IABP were shown to be powerful independent predictors of CIN [29]. In our study, IABP was used only in two patients (0.8%) and one of them developed CIN, but it failed to reach statistically significance [p=0.188].

Study limitations: (a) non randomized study, (b) small sample size, data derived from a single hospital, (c) the absence of data on serum creatinine later than 48 h after PCI in the present study might result in the slight underestimation of CIN, (d) long term follow up of CIN patients is not available.

CONCLUSION

The incidence of CIN increases with the increase in number of associated risk factors, as every risk factor had cumulative effect to cause CIN. As volume of contrast agent increases, CIN incidence increases exponentially. Every effort should be made to prevent CIN by recognizing at risk population as there is no well established treatment for CIN. CIN can even occur with small (30 ml) volume of contrast, ruling out threshold effect. Hence, all patients should be categorized based on the Mehran's risk score and whenever a patient's MRS is found to be >10 [preprocedure], lowest dose of contrast should be used along with maintaining adequate hydration in periprocedural period, avoid nephrotoxic medications and whenever indicated [particularly in diabetes mellitus and chronic kidney disease patients] staged procedure or CABG should be planned, thereby decrease contrast exposure to minimum at a time. The best measures to prevent CIN is to identify the patient at risk, provide adequate periprocedural hydration and minimize the amount of contrast.

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