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THE INCIDENCE AND RISK FACTORS OF CONTRAST INDUCED NEPHROPATHY AND THE APPLICABILITY OF THE MEHRAN'S RISK SCORE IN PATIENTS UNDERGOING CORONARY INTERVENTIONS.

Cardiology

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ABSTRACT

Objectives: To determine the incidence of contrast induced nephropathy (CIN) and to study the applicability of the Mehran's Risk Score (MRS) in the prediction of CIN in our population.

Patients and Methods: A total of 250 patients (186 males and 64 females) who received non ionic iso osmolar contrast media during PCI were included in the 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 and the MRS used to accurately predict the incidence of CIN in patients belonging to the respective risk group.

Results: The overall incidence of CIN was 16%. In univariate analysis: age >75 years, diabetes mellitus, heart failure, hypotension, CKD [creatinine >1.5mg/dl] and increased contrast volume predicted a trend towards risk of CIN whereas anemia, gender and IABP failed to reach statistically significance. As MRS increases, the incidence of CIN increases with 11.25%, 17.24%, 32% and 57.14% for low, intermediate, high and very high risk group respectively.

Conclusion- CIN is related with many risk factors, so whenever a patient's MRS is found to be >10 [preprocedure], lowest dose of contrast should be used by incorporating "maximal allowable contrast (MAC) dose" as a part of pre-procedure contrast 'Time-Out' and measures for the prevention of CIN should be taken.

KEYWORDS

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

INTRODUCTION

The use of intravascular iodinated contrast agents has continued to increase over recent years. Contrast induced nephropathy [CIN] is an iatrogenic renal injury that follows administration of radio-opaque contrast media in susceptible individuals. CIN is widely recognised as the third most common cause of hospital acquired acute kidney injury (AKI) after renal hypoperfusion and the use of nephrotoxic medications and accounts for 11% to 12% of all cases of in hospital AKI with in hospital mortality rate of 6% [1,2,3]. It is important to exclude other causes of AKI as small rises in serum creatinine have been demonstrated to occur in 8 to 35% of patients admitted to hospital without exposure to contrast media [4]. Among all procedures utilizing contrast media for diagnostic or therapeutic purposes, coronary interventions are associated with the highest rates of CIN [2]. Most cases of CIN are self limiting with serum creatinine levels returning to baseline within 2 weeks [5, 6]. It should be noted that the well validated MRS was formulated in a western population where the incidence of CIN was found to be 13.1% [7]. Our patients have higher atherogenic burden with a higher incidence of risk factors for CIN.

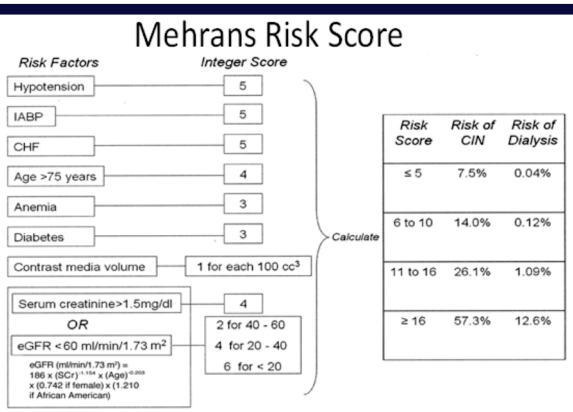
CIN: AKI in the setting after contrast media administration derives from many causes including ischemia, atheroembolism or nephrotoxicity of the contrast itself. The latter is referred to as CIN. The most accepted definition is that of the European Society of Urogenital Radiology (ESUR) which defines 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]. Diagnosing CIN is challenging, as it is a diagnosis of exclusion after other causes of AKI (prerenal /intrinsic /post renal) have been ruled out. CIN was diagnosed when an increase in serum creatinine by >25% or an absolute increase of 44.2 mmol/l [0.5 mg/dl] occur within 2 days after intravascular administration of contrast medium.

Exclusion criteria: Patients having a history of allergic reaction to contrast agents or iodine, patients with serum creatinine >2mg/dl, patients who were on a dialysis regimen, pregnancy, active malignancy, patients who did not have a pre-procedure serum creatinine level analysis, patients with post procedure serum creatinine level analysis not done at the same reference laboratory and patients with single functional kidney.

Risk prediction scores for CIN: There are numerous risk scores for the prediction of CIN in patients undergoing interventions with radio-contrast media [9, 10]. Of these simple risk scoring, which has shown to have clinically significant predictive value for CIN, is ACEF score. It uses 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 well validated in external populations other than in India and is provided with an online calculator. The only weakness with the MRS is that it can only be calculated once the procedure is complete.

MATERIAL AND METHODS

We prospectively enrolled 250 consecutive patients (age ≥ 18 years) with the diagnosis of coronary artery disease (CAD) or the worsening symptoms in patients with known history of coronary artery disease (CAD) who were admitted to undergo PCI, between january 2017 to december 2018 at a tertiary care hospital in north India. Clinical history taken and blood samples were obtained at admission and at 48 hours after the PCI(percutaneous coronary intervention). Nephrotoxic drugs if any, being used, and metformin was stopped 24 hours before the procedure. A nonionic, iso osmolar contrast medium (iohexol) was the sole contrast agent used. Following the procedure, serum creatinine levels were obtained from the same reference laboratory where preprocedure serum creatinine levels were determined to negate the inter laboratory variability in the measurements of serum creatinine levels. Post procedure serum creatinine levels thus obtained were compared with the pre procedure levels to determine whether CIN had occurred or not. We evaluated incidence of CIN, need for dialysis and CIN related mortality during index hospitalisation and the MRS used to accurately predict the incidence of CIN in patients belonging to



Scheme to define CIN risk score. CHF denotes congestive heart failure class III–IV by the New York Heart Association classification and/or history of pulmonary edema. eGFR denotes estimated glomerular filtration rate by Modification of Diet in Renal Disease formula. Anemia: baseline hematocrit value of 39% for men and of 36% for women. Hypotension: systolic blood pressure of 80 mm Hg for at least 1 h requiring inotropic support with medications or IABP within 24 h periprocedurally.

RESULTS

In current study, all 250 patients were adults with age ranging from 18 to 85 years. CIN occurred in 40 (16%) patients.

Table 1. Baseline parameters and comparison between patients with and without CIN

Risk factors		Patient %	CIN %	Relative risk	P value
Age > 75	Yes	32 (12.8%)	12 (37.5%)	2.92	<0.001
	No	218 (87.2%)	28 (12.84%)		
Gender	Male	186 (74.4%)	33 (17.7%)	1.62	0.2
	Female	64 (25.6%)	7 (11%)		
Anemia	Yes	55 (22%)	10 (18.2%)	1.18	0.617
	No	195 (78%)	30 (15.4%)		
Creatinine > 1.5	Yes	18 (7.2%)	8 (44.44%)	3.22	0.001
	No	232 (92.8%)	32 (13.8%)		
CHF	Yes	38 (15.2%)	11 (28.95%)	2.116	0.018
	No	212 (84.8%)	29 (13.68%)		
DM	Yes	45 (18%)	15 (33.33%)	2.733	<0.001
	No	205 (82%)	25 (12.2%)		
Hypotension	Yes	25 (10%)	10 (40%)	3	0.001
	No	225 (90%)	30 (13.33%)		
IABP	Yes	2 (0.8%)	1 (50%)	0.319	0.188
	No	248 (99.2%)	39 (15.7%)		

The various risk factors evaluated in our study were age, gender, anemia, hypotension, volume of contrast, congestive heart failure, intra-aortic balloon pump, DM and preprocedural serum creatinine levels. There was a male predominance observed in our study, with 186 (74.4%) were males and 64 (25.6%) were females, the male : female ratio was 3:1. Table 1 showing univariate analysis of binary logistic regression for the dependent variables.

Table:-2 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	160 (64 %)	18 (11.25%)	0.0063	0%	---
6-10	Intermediate	58 (23.2%)	10 (17.24%)	0.769	0%	---
11-16	High	25 (10%)	8 (32%)	0.021	1 (4%)	<0.001
>16	Very high	7 (2.8%)	4 (57.14%)	0.003	1 (14.28%)	<0.001

As MRS increases, incidence of CIN increases with 11.25%, 17.24%, 32% and 57.14% for low, intermediate, high, and very high risk respectively(table 2). Similarly as MRS increases the need for dialysis increases, with high score showing 4% and very high risk score showing 14.28% patients required dialysis in current study [p= <0.05]. The mean MRS of the study population was 6.42. It was observed that a majority of the patients {64%, n = 160} belonged to the low MRS (<5). Another 32 patients (12.8%) had a high MRS of more than 10. In univariate analysis age >75 years, DM, CHF, hypotension, CKD [creatinine>1.5mg/dl] and increased contrast volume predicted a trend towards risk of CIN among patients undergoing PCI. Among those patients who developed CIN post procedure, two required hemodialysis (5%) and one patient died of sudden cardiac arrest (2.5%) in hospital.

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

Contrast in ml	Total patient	Patient without CIN	Patient with CIN	P value
<100 ml	[65]	63 (96.9%)	2 (3.1%)	<0.001
100-200 ml	[110]	94 (85.45%)	16 (14.54%)	
200-300ml	[55]	41 (74.54%)	14 (25.45%)	
300-400 ml	[20]	12 (60%)	8 (40%)	

As volume of contrast increases, there is exponential increase in CIN incidence (table 3). In our study the mean volume of contrast administered was significantly higher in CIN group (P < 0.001). There was statistically significant difference in whether procedure completed in < 100 ml or >100ml [p=0.0044].

DISCUSSION

In our study, we used a CIN risk stratification score based on eight readily available variables, and we observed that an increasing score number confers exponentially increased CIN risk. The incidence of CIN quoted in the literature varies widely. The two larger studies, which included 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 overall incidence of CIN in our study was 16%.

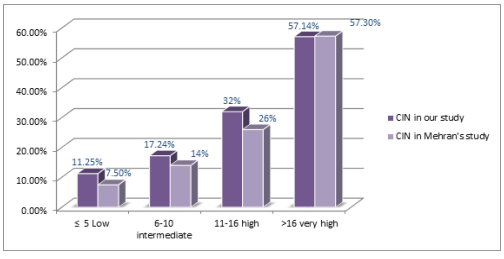


Fig 1 Figure showing comparision of CIN in current study versus risk of CIN based on MRS.

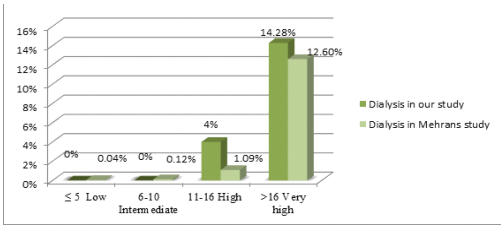


Fig 2 showing comparision of risk of dialysis in current study versus based on MRS.

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 and 2 showing comparision of incidence CIN and need for dialysis in our study and MRS respectively. When the patients were subclassified based on the Mehran risk score {MRS} it was seen that 18 patient [11.25%] with an MRS <5 developed CIN. The incidence of CIN in the high risk group with MRS of 11 to 15 was 3 fold higher, [p = 0.0214] compared to the group with MRS of <5. Within each subcategory of MRS, the observed incidence of CIN in our study was higher than the expected risk based on the MRS. The incidence of CIN in very high risk group [>16] was similar in our study and reference group in MRS (Fig 1).

Advanced age is a risk factor for the occurrence of CIN [16]. Ageing predispose patients to renal sodium and water wasting due to reduction in renal mass, function, and perfusion. The study by Mehran et al in 2004 puts (12) the incidence at as high as 21.8% among those aged >75 years [17]. The incidence of CIN in the elderly being higher than younger individuals in our study (37.5% vs. 12.84%), and it did achieve statistical significance (P < 0.001).

In one study female sex was an independent predictor of CIN [17], while in another study male gender was an independent risk factor for CIN [5]. However, we were not able to observe any statistically significant gender preponderance [p= 0.2].

Preexisting renal insufficiency is the most important and predictive risk factor for CIN. We found that the baseline serum creatinine levels of those who developed CIN were higher than those who did not develop CIN (p=0.001). 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 44.44% patients with creatinine >1.5mg/dl. Two patients (5%) who developed CIN, required hemodialysis and one out of 40 patients (2.5%) died after developing CIN, 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.

Heart failure predisposes to increased risk of CIN. In the studies done by Rihal et al [19] and Bartholomew et al [20] CHF was an independent risk factor for CIN. The incidence of CIN in CHF group in our study was 28.95% [p < 0.018].

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]. However, we did not observed such association in our study, possibly because mild anemia (mean Hb 11.44 mg/dl) may not cause statistically significant difference in CIN [P=0.617], also adequate hydration was given and nephrotoxic drugs were avoided.

In Diabetic patients nitric oxide dependent renal vasodilation is characteristically altered, and the renal outer medullary pO2 is significantly reduced [23]. DM was found to predict CIN only if there was associated 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 33.33% [p < 0.001].

The volume of contrast is a main modifiable risk factor in the development of CIN. In our study iodine content of contrast ranges from 300 to 370 mg/ml. As volume of contrast increases, there is exponential increase in CIN incidence in our study (P < 0.001) (table 3). Volume of contrast administered was directly linked to the occurrence of CIN in the present study as already established [7]. Low dose of contrast 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 [ml = 5 × body weight {kg}]/ [88.4 × SCr {μmol/l}]), which correlated, with development of CIN [26]. Various studies have a positive correlation between volume of contrast injected and risk of development 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 during IABP insertion, counterpulsation or removal (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 and (c) as a marker of increased vascular complications and post-PCI hypotension. Peri PCI hypotension 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) contrast volume used in a wide range [100ml] in risk scoring, d) 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, e) long term follow up of CIN patients is not available.

CONCLUSION

CIN is a marker for increased mortality. Short hospital duration decreases the awareness of and preventive treatment of CIN. What so ever the scoring system we use, and what so ever our score is, and what weightage we give to contrast volume, CIN require contrast media to occur. CIN can even occur with small (30 ml) volume of contrast, ruling out threshold effect. So, 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 by incorporating MAC as a part of preprocedure contrast 'Time-Out' and measures for the prevention of CIN should be taken. The best approach to prevent CIN is to identify the patient at risk, provide adequate periprocedural hydration and minimize the amount of contrast.

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