

THE INCIDENCE AND RISK FACTORS OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CORONARY ANGIOPLASTY.

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Abstract

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

Objectives: To determine the incidence and to study the various risk factors associated with CIN.

Patients and Methods: In our study, total of 212 patients (154 males and 58 females) who received non ionic iso osmolar contrast media during percutaneous transluminal coronary intervention were included. We diagnosed CIN by a relative increase of >25% or an absolute increase of >0.5 mg/dl in serum creatinine levels two days after procedure.

Results: The incidence of CIN in our study was 15.1%. In univariate analysis: age >75 years, hypertension diabetes mellitus (DM), heart failure, hypotension, CKD [creatinine >1.5mg/dl] and increased contrast volume were associated with increased risk of CIN whereas, gender, anemia and use of IABP failed to reach statistical significance. As the number of risk factor and/or volume of contrast increases, the incidence of CIN increases exponentially. **Conclusion:** Since there is no established treatment for CIN, all possible efforts should be taken to prevent it from occurring by identifying patients at risk. CIN is related with many risk factors, so whenever multiple risk factors are present in an individual patient, lowest dose of contrast should be used and adequate hydration should be given.

Key Words: Contrast-induced nephropathy, Non ionic iso-osmolar contrast media, percutaneous coronary intervention.

Introduction

Contrast induced nephropathy (CIN) is iatrogenic deterioration of renal function following intravascular contrast media administration in the absence of other nephrotoxic event. CIN is widely recognised as the third most common cause of hospital acquired acute kidney injury (AKI) [1]. Ruling out other causes of AKI is necessary, as small rise in serum creatinine occur in 8 to 35% of hospitalized patients without exposure to contrast media [2]. Among all procedures for diagnostic or therapeutic purposes, PCI were associated with the highest rate of CIN [1]. The serum creatinine typically rises in 3–5 days after exposure to contrast media and returns to baseline within 1–3

weeks [3]. Thus most cases of CIN are self limiting, however in patients with multiple risk factors for CIN, it can leads to morbidity and even mortality [4]. Reported incidence of CIN in various studies were between 2% and 50%, depending upon the definition of CIN used [4, 5, 6]. Many risk factor influences CIN, so every known risk factor should be analyzed, because as the number of risk factors increase cumulative risk increases [7]. Identification of patients at risk for CIN is important. Risk factors are broadly classified as :- Non-modifiable, includes CKD, DM, elderly, heart failure and shock, while volume of contrast, nephrotoxic medications, hypotension,

dehydration, anemia and intra-aortic balloon pump (IABP) insertion represent the modifiable risk factors.

Aims and objectives: In our study, we evaluated the incidence of CIN at our centre, significance of various risk factors, need for hemodialysis and CIN related in hospital mortality.

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]. CIN is a diagnosis of exclusion, after other causes of AKI (prerenal/ intrinsic/ post renal) have been ruled out.

Exclusion criteria : a) Allergic reaction to contrast agents or iodine, b) Serum creatinine >2mg/dl, c) Patients on hemodialysis regimen, d) Patients with single functional kidney, e) Pregnancy, f) Patient with pre and post procedure serum creatinine level analysis done from different laboratory.

MATERIAL AND METHODS

In our study we enrolled 212 consecutive patients (age \geq 18 years) of coronary artery disease (CAD) who were admitted to undergo PCI, between march 2018 to february 2019 at a tertiary care hospital in north

India. Clinical history taken and blood samples were obtained at the time of admission and at 48 hours after the PCI. Nephrotoxic drugs including metformin were stopped 24 hours prior to the procedure. Nonionic iso osmolar contrast medium (iohexol) was the sole contrast agent used. Pre and post procedure serum creatinine level analysis done from the same reference laboratory to avoid the inter laboratory variability. We diagnosed CIN by 25% relative increase, or a 0.5 mg/dl (44 μ mol/L) absolute increase in serum creatinine after 48 hours of contrast exposure, in the absence of an alternative cause.

Statistical Analysis: Continuous variables were expressed as mean, standard deviation (SD), and qualitative data were presented as percentages. Chi-square test was used to determine any significant difference between two groups. p value of less than 0.05 was considered significant. The statistical analyses were performed with SPSS software (version 16.0)

RESULTS

In our study, all 212 patients were adult, with age between 18 to 85 years. The mean age of patients was 63.42 ± 12.36 years with 154 (72.64%) male and 58 (27.36%) were female. The male female ratio was 2.65:1. CIN occurred in 32 (15.1%) patients [fig 1].

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

Risk factors		Patient %	CIN %	Relative risk	P value
Age > 75	Yes	27 (12.74%)	9 (33.33%)	2.68	0.0046
	No	185 (87.26%)	23 (12.43%)		
Gender	Male	154 (72.64%)	19 (12.34%)	0.55	0.0677
	Female	58 (27.36%)	13 (22.4%)		
Anemia	Yes	43 (20.3%)	8 (18.6%)	0.76	0.471
	No	169 (79.7%)	24 (14.2%)		
Creatinine > 1.5 mg/dl	Yes	17 (8.02%)	7 (41.2%)	3.21	0.0017
	No	195 (91.98%)	25 (12.82%)		
CHF	Yes	41 (19.34%)	12 (29.3%)	2.5	0.0048
	No	171 (80.66%)	20 (11.7%)		
DM	Yes	38 (17.3%)	11 (28.95%)	2.40	0.0085
	No	174 (82.1%)	21 (12.1%)		
Hypotension	Yes	25 (11.8%)	10 (40%)	3.4	0.0002
	No	187 (88.2%)	22 (11.76%)		
IABP	Yes	2 (0.94%)	1 (50%)	0.29	0.166
	No	210 (99.06%)	31 (14.76%)		
Hypertension	Yes	40 (18.87%)	11 (27.5%)	2.25	0.015
	No	172 (81.13%)	21 (12.21%)		
Contrast >100 ml	Yes	70 (33.02%)	23 (32.9%)	5.18	< 0.001
	No	142 (66.98%)	9 (6.34%)		

The various risk factors evaluated in our study were age, gender, anemia, hypertension, hypotension, volume of contrast, congestive heart failure, intra-aortic balloon pump, DM and preprocedural serum creatinine levels. Table 1 showing univariate analysis of binary logistic regression for the dependent variables. In univariate analysis age >75 years, hypertension, DM, CHF, hypotension, CKD [creatinine>1.5mg/dl] and increased contrast volume were associated with increased risk of CIN whereas, gender, anemia and use of IABP failed to reach statistical significance among patients undergoing PCI. In our study, the relative risk of developing CIN was higher with large volume of contrast used, periprocedural hypotension and preexisting renal insufficiency [Table 1].

Table 2: Baseline characteristics of the patients

Variables	Mean ± SD
Age in years	63.42 ± 12.36
Hemoglobin mg/dl	11.6 ± 1.32
Creatinine mg/dl	1.21 ± 0.42
Contrast in ml	102.84 ± 35.86

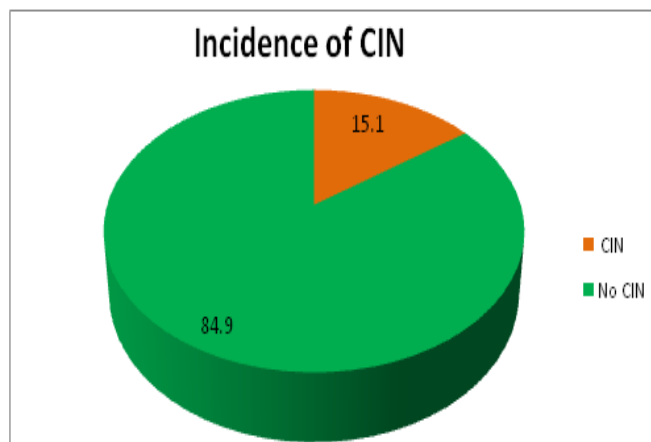


Figure 1: The pie diagram showing the incidence of CIN after coronary intervention.

Table 3: The split up of the patients based upon the number of risk factors.

Risk factors	Patients without CIN N=180	Patients with CIN N=32	Total patients	P Value
0	92 (97.87%)	2 (2.13%)	94 (44.34%)	0.0001
1	62 (92.54%)	5 (7.463%)	67 (31.6%)	0.035
2	22 (68.75%)	10 (31.25%)	32 (15.1%)	0.006
≥3	4 (21.05%)	15 (78.95%)	19 (8.96%)	0.00012

The independent risk factors for CIN in our study were, age >75 years, hypertension, DM, CHF, hypotension, CKD [creatinine>1.5mg/dl] and increased contrast volume. Only two patients (2.13%) out of ninety four with no risk factor developed CIN, whereas fifteen patients (78.95%) with three or more risk factors developed CIN, suggesting as the number of risk factors increases, there was exponential increase in CIN incidence [table 3, fig 2].

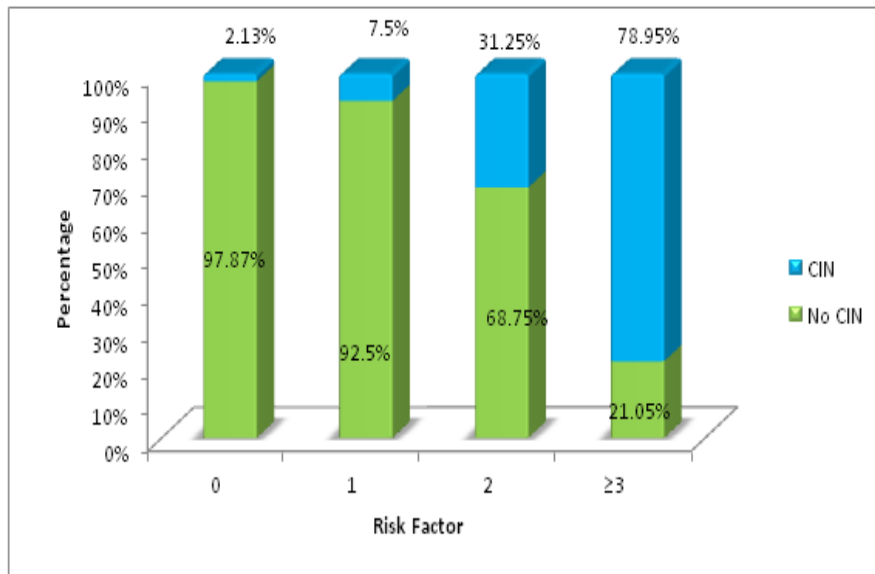


Figure 2: showing proportion of patients developed CIN as number of risk factors increases.

Table 4: showing comparison of CIN with variable volume of contrast and variable risk factors.

Risk factors	Contrast volume >100ml		Contrast volume ≤100ml		P value
	Total patients	Patients with CIN	Total patients	Patients with CIN	
≥3	12	10 (83.33%)	7	5 (71.43%)	0.54
2	15	8 (53.33%)	17	2 (11.76%)	0.0113
0-1	43	5 (11.63%)	118	2 (1.7%)	0.0062

In patients with three or more risk factors, the incidence of CIN was higher [83.33%] if more than 100 ml contrast given compared to [71.43%] patients with less than 100 ml contrast used. However these differences were not statistically significant suggesting multiple risk factors makes patients susceptible to CIN even on <100 ml of contrast exposure. In patients with two or less than two risk factors there was consistently lower incidence of CIN in patients with lesser [<100 ml] volume of contrast used, suggesting small volume of contrast causes fewer cases of CIN in patients with lesser number of risk factors and vice versa [table 4].

Table 5: showing relation between contrast volume and development of CIN.

Contrast volume in ml	Patient without CIN N=180	Patient with CIN N=32	Total Patients	P Value
50 -100 ml	133 (93.66%)	9 (6.34%)	[142]	< 0.001
101-150 ml	26 (78.79%)	7 (21.21%)	[33]	0.285
151-200ml	16 (61.54%)	10 (38.46%)	[26]	0.0004
201-250 ml	5 (45.45%)	6 (54.54%)	[11]	0.0002

As volume of contrast increases, there was increase in CIN incidence exponentially (table 5). CIN detected in 6.34% of patients if procedure completed in 100ml compared to 54.54% developed CIN if contrast volume of more than 200ml was used. In our study the mean volume of contrast administered was significantly higher in CIN group (P < 0.001).

DISCUSSION

The incidence of CIN mentioned in the literature varies widely. The two larger studies of 7586 and 8628 patients undergoing PCI reported incidences of CIN of 3.3% and 16.5%, respectively [9, 10]. The incidence of CIN in our study was 15.1%. The higher incidence of CIN in our study was due to aggregation of multiple risk factors in our patients, also complex PCI including CTOs were attempted.

Advanced age is a non modifiable risk factor for the occurrence of CIN [11]. Ageing predispose patients to renal salt and water wasting due to reduction in renal mass, function, and perfusion [12]. The study by Mehran et al in 2004 puts the incidence at as high as 21.8% among those aged >75 years [10]. The incidence of CIN in our study in the elderly patients was higher than younger individuals (33.33% vs 12.43%) and it did achieve statistical significance ($P < 0.0046$).

In a study by Iakovou I et al female sex was an independent predictor of CIN [10], while in another study by Rudnick MR et al male gender was independently associated with occurrence of CIN [13]. However, in our study there was no gender preponderance [$p = 0.0677$].

Preexisting renal insufficiency is one of the most important risk factor for CIN. In our study the mean creatinine level of patients undergoing PCI was 1.21 ± 0.42 mg/dl [table 2]. The baseline serum creatinine levels of those who developed CIN were higher ($p = 0.0017$). The incidence of CIN in CKD patients was extremely high, ranging from 14.8 to 55% [4, 14]. In our study CIN occurred in 41.2% patients with creatinine >1.5 mg/dl. Out of two patients (6.25%) who developed CIN and required hemodialysis, one finally recovered his renal function after prolonged hospital stay but another one (3.125%) died because of sudden cardiac arrest in hospital, although, it was difficult to establish that CIN was actually the cause of the death in that patient, CIN at the very least is a marker for increased morbidity and mortality.

Heart failure predisposes the patient to increased risk of CIN, possibly due to decrease in effective circulatory volume, inadequate diuresis and release of vasoconstrictor substances [15]. In the studies done by Rihal et al [16] and Bartholomew et al [17] CHF was an independent risk factor for CIN. The incidence of CIN in CHF patients in our study was 29.3% [$p < 0.0048$].

A baseline hematocrit value $< 39\%$ for man and $< 36\%$ for woman is a risk factor for developing CIN [18]. However, we did not observed such association in our study, possibly because mild anemia (mean hemoglobin 11.6 ± 1.32 mg/dl) may not cause statistically significant difference in CIN [$P = 0.47$].

Diabetes predict CIN only if there was associated diabetic microangiopathy [19]. The incidence of CIN in diabetic patients varies from 5.7 to 29.4% [20]. In our study incidence of CIN in DM was 28.95% [$p < 0.0085$].

Hypertension is a significant risk factor for the occurrence of CIN [17, 21], as it is usually associated with advanced atherosclerosis of the aorta and suggests that atheroembolization to the kidney during procedure causes AKI [22]. Hypertension induced endothelial injury could be one of the predisposing factors for the CIN [23]. In our study incidence of CIN in hypertensive patients was 27.5% [$p < 0.015$].

The contrast volume is a main modifiable risk factor for CIN. In our study the mean volume of contrast used per patient was 102.84 ± 35.86 ml. As volume of contrast increases, there was exponential increase in CIN incidence in our study ($P < 0.001$) as already established [24]. IABP insertion may be linked with CIN via (a) atheroemboli to the kidney during IABP use (b) it may partially occlude renal blood flow if positioned too low in the aorta. Periprocedural hypotension and use of IABP were shown to be powerful independent predictors of CIN [15]. In our study, IABP was used only in two patients (0.94%) and one of them developed CIN, but it failed to reach statistical significance [$p = 0.166$].

Study limitations: a) non randomized study, b) small sample size, data obtained from a single hospital, c) the absence of data on serum creatinine later than 48 h after PCI might result in underestimation of CIN incidence, d) No long term follow up of CIN patients, e) rare risk factors [hyperuricemia, multiple myeloma etc] were not included in our study, f) other markers of renal injury like Cystatin-c, KIM-1, NGAL were not used.

CONCLUSION

Our study highlights the few important facts. Most importantly, the incidence of CIN in patients with multiple risk factors undergoing PCI was as high as 83.33% particularly if large volume of contrast used, and not necessarily decreases by decreasing contrast

volume. There was significant increase in CIN incidence with increasing risk factors, as every risk factor had cumulative effect to cause CIN. Lastly as volume of contrast increases, CIN incidence increases exponentially. Since there is no well established treatment for CIN, every effort should be taken to prevent it by recognizing at risk population, weighing risk-benefit ratio of procedure in all patients. Maintain adequate hydration in periprocedural period, avoiding nephrotoxic medications and whenever indicated [particularly in diabetes mellitus and chronic kidney disease patients] staged procedure or CABG, manage accordingly, thereby decrease contrast exposure to minimum at a time.

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