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Renal complications in contrast studies

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Abstract
Objective: To evaluate the effect on renal function, assess the outcome in patients undergoing contrast based procedures and establish relationship of comorbidities with contrast induced nephropathy (CIN).
Material and Method: A cross-sectional observation study conducted on 1100 patients admitted in a tertiary hospital was included. Patient's baseline and post-procedure creatinine were obtained to estimate the incidence of contrast induced nephropathy.
Result: 27.3% of study population were observed to have CIN, with an increased risk in those with high BMI and those above the age of 40 years. Statistically significant proportion of female population was observed to have CIN. Hypertension and combination of comorbid conditions was significantly associated with CIN. A linear relationship was observed between dose and CIN. Gadolinium based contrast media was found to be safer as compared to iodine based contrast media. Positive cases had a significantly higher baseline and post-procedure serum creatinine and eGFR values ($p<0.001$)
Conclusion: Pre-existing renal impairment plays a significant role in CIN and should be considered as a major pre-disposing factor. Hypertension, Diabetes Mellitus and those on nephrotoxic nonsteroidal anti-inflammatory drugs have a direct effect on the renal functioning and hence. Being a dose-dependent phenomenon, gadolinium based contrast media are safer than iodine based contrast media. In India, not many studies have been performed to know the incidence of CIN. This study focuses on studying the incidence and risk factors associated with contrast induced nephropathy.

Keywords: gadolinium contrast, iodine contrast, nephropathy, creatinine

1. Introduction

Contrast-induced nephropathy (CIN) is defined as the impairment of renal function—measured as either a 25% increase in serum creatinine (SCr) from baseline or a 0.5 mg/dL (44 μmol/L) increase in absolute SCr value—within 48-72 hours of intravenous contrast administration.

For renal insufficiency (RI) to be attributable to contrast administration, it should be acute, usually occurring within 2-3 days (although it has been suggested that RI up to 7 days post–contrast administration be considered CIN); it should also not be attributable to any other identifiable cause of renal failure. Following contrast exposure, SCr levels peak between 2 and 5 days and usually return to normal in 14 days. CIN is one of the leading causes of hospital-acquired acute kidney injury. It is associated with a significantly higher risk of in-hospital and 1-year mortality, even in patients who do not need dialysis [1].

Multiple risk factors may contribute to the development of CIN, patient- and procedure-related.

Pre-existing renal insufficiency (estimated glomerular filtration rate (eGFR) <60 ml/min) and diabetes mellitus are the most important patient-related risk factors. Others, include age >75 years, uncontrolled hypertension, hypotension requiring inotropes, congestive heart failure (CHF), use of intra-aortic balloon pump (IABP), anaemia, hypoalbuminemia, and liver cirrhosis.

Procedure-related factors include high contrast volume, osmolality, and repeated exposures to CM within 72 h. Other factors that may increase the risk of CIN include the concomitant use of diuretics or nephrotoxic drugs (NSAIDs) and aminoglycosides. Although the definite mechanism of CIN is not well-understood, several mechanisms have been proposed like renal medullary hypoxia, direct toxicity of CM which could be related to harmful effects of free radicals and oxidative stress and apoptosis. There are 3 types of contrast media agents, namely iodinated (iodine based), gadolinium based and barium sulphate. Barium sulphate is used for barium swallow, whereas iodinated and gadolinium are commonly used for MRI screening, computed tomofigy, coronary angiofigic procedures. Evidence suggests that, compared to iodinated CM, gadolinium contrast is associated with a significantly lower incidence of contrast nephropathy. A study conducted by Kane *et al.* to study the clinical outcomes when iodinated contrast medium and gadolinium based agents were used for percutaneous intervention suggested that gadolinium was associated with a substantially

lower incidence of deteriorating kidney function (5.3%) as compared to iodinated contrast (20.6%) [2].

Methods and material

In a tertiary hospital based in western Maharashtra a prospective, descriptive, analytical, observational study of 1100 patients, above the age of 18 year-old, admitted in the ward or visiting the outpatient clinic of the hospital for undergoing contrast based procedures were assessed for the effect of contrast agents on renal function. Serum creatinine levels prior to the procedure and on 3rd day after the procedure were recorded to identify the incidence of contrast induced nephropathy (CIN). Various risk factors associated with CIN were identified to establish their association with the degree of renal impairment. The proportion, prevalence of CIN and risk ratios for the risk factors were calculated using standard statistical methods. Various procedures such as angiofigy, angioplasty, CT Brain, CT pulmonary/ angiofigy, CT abdomen/pelvis, CT brain, HRCT thorax and MRI brain using iodine based or gadolinium based contrast media were studied for the incidence of contrast induced nephropathy and the associate risk factors.

Result

Out of total study population of 1100 cases, 27.3%(300cases) had and 800 cases (72.7%) did not have CIN. 94.3% cases in the age group 61-80 years had CIN which was significantly higher (P-value<0.001) suggestive of age as a major risk factor. The incidence of CIN among males is 26.8% and in females it is 28.1%, the difference was not statistically significant (P-value>0.05) Pre-obese (53%) and obese patients (94.7%) patients had higher incidence of CIN, suggestive of weight as a risk factor for CIN.

Hypertension and mixed comorbid conditions were significantly associated with CIN (p<0.001). 56.3% of chronic NSAID users were diagnosed with CIN, hypertension cases 55% and Diabetes Mellitus 23.7%. (Table1).

A total of 39.9% of those who underwent angiofigy, 32.7% with angioplasty, 26.3% with CT Brain were found to have contrast induced nephropathy; whereas on the other hand, only 18.5% of those with CT KUB were reported to have CIN. The incidence of CIN is significantly higher among the cases with procedures such as Angiofigy, Angioplasty, CT brain, CT Abdomen/Pelvis contrast procedures (P-value<0.001).(Table 2)

The baseline mean serum creatinine levels of positive cases was 0.92mg/dL, whereas the mean of negative cases was 0.77mg/dL.The distribution of pre and post-procedure mean e-GFR is significantly higher in CIN negative cases compared to those which were CIN positive.

Overall, the procedures using gadolinium based contrast media had lower incidence of CIN as compared to iodine based contrast media. 26.3% of patients with procedures requiring low-osmolar iodine based contrast media and 28.3% of those with iso-osmolar and only 21.3% of those with gadolinium based contrast procedures were observed to have CIN. (Fig 1) The incidence of CIN did not differ significantly across various contrast media or with iodinated contrast media used among the cases studied (P-value>0.05). A high dose of 70-90ml of contrast media resulted in 34.8% positive cases; whereas only 21.3% of positive cases in low-dose contrast media suggested that, CIN is a dose dependent phenomenon.(Fig 2) The incidence of CIN is significantly higher among the cases who required relatively higher dosages of contrast media (P-value<0.001).

Legends

Table 1: Distribution of incidence of contrast induced nephropathy (CIN) according to Co-morbidity.

	CIN Positive		CIN Negative			P-value
Co-Morbidity	**n**	**%**	**n**	**%**	**Total**	**0.001**
Nil	43	7.0	568	93.0	611	100.0
Chronic NSAID use	18	56.3	14	43.7	32	100.0
Diabetes	23	23.7	74	76.3	97	100.0
Hypertension	66	55.0	54	45.0	120	100.0
Mixed	129	58.9	90	41.1	219	100.0
Pre-existing renal impairment	21	100.0	0	0.0	21	100.0
Total	300	27.3	800	72.7	1100	100.0

Values are n (% of cases). P-value by Chi-Square test. P-value less than 0.05 is considered to be statistically significant. ***P-value<0.001 (Highly Significant).

Table 2: Distribution of incidence of contrast induced nephropathy (CIN) according to Contrast procedure. CIN Status

Contrast Procedure	**Positive**		**Negative**		**P value**	**0.001****
	N	**%**	**N**	**%**	**Total**	
Angiofigy	82	39.9	140	63.1	222	100.0
Angioplasty	73	32.7	150	67.3	223	100.0
CT Abdomen/Pelvis	34	25.4	100	74.6	134	100.0
CT Brain	10	26.3	28	73.7	38	100.0
CT KUB	30	18.5	132	81.5	162	100.0
CT Pulmonary Angiofigy	14	23.0	47	77.0	61	100.0
HRCT Thorax	25	22.7	85	77.3	110	100.0
MRI Brain	32	21.3	118	78.7	150	100.0
Total	300	27.3	800	72.7	1100	100.0

CT- Computed Tomofigy
KUB- Kidney Ureter Bladder
HRCT- High Resolution Computed Tomofigy
MRI- Magnetic Resonance Imaging

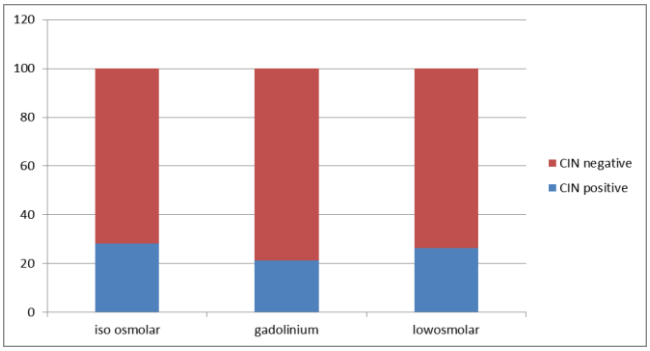

Fig 1: Distribution of incidence of contrast induced nephropathy (CIN) according to Contrast media

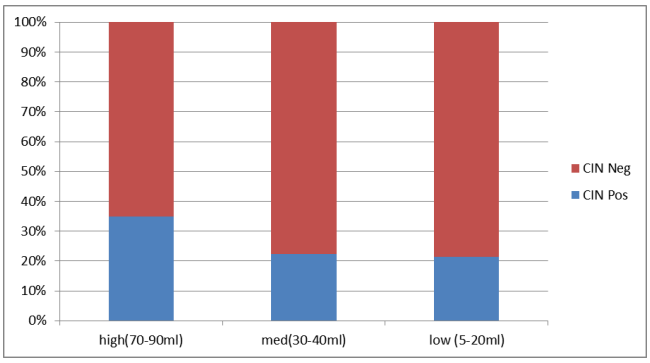

Fig 2: Distribution of incidence of contrast induced nephropathy (CIN) according to dose of Contrast media.

Discussion

Out of total study population of 1100 cases, 27.3% had and 72.7% did not have CIN. 94.3% cases in the age group 61-80 years had CIN which was significantly higher (P-value<0.001) suggestive of age as a major risk factor. Multivariate analysis revealed a relationship between an absolute increase in SCr ≥ 0.5 mg/dL and old-age [3]. Suchi Bhatt *et al*. in their study of 250 patients undergoing IV iodinated CM report that the demofigic variables like age and weight were homogenous in both CIN positive and CIN negative groups indicating no role in the occurrence of CIN [4]. In our study also the incidence of CIN among males is 26.8% and in females it is 28.1%, the difference was not statistically significant (P-value>0.05)

A study conducted in Sao Paulo, with 361 patients, showed that 35% of the elderly presented with AKI (Acute kidney Injury) due to the use of contrast for radiologic examinations [5].

When stratified by BMI, obesity was not found to be associated with the development of AKI or CN after exposure to radiocontrast [6].

However in our study the pre-obese (53%) and obese patients (94.7%) patients had higher incidence of CIN, suggestive of weight as a risk factor for CIN.

Hypertension and mixed comorbid conditions were significantly associated with CIN (p<0.001). 56.3% of chronic NSAID users were diagnosed with CIN, hypertension cases 55% and Diabetes Mellitus 23.7% in our study. Parfrey *et al*. in a prospective trial of patients with diabetes, showed that none of 85 patients with diabetes and normal renal function developed clinically significant renal impairment [7]. Ergu¨n I *et al*. analysed 473 patients approximately 20% of patients had diabetes mellitus, and 80% had hypertension. Eleven of 91 patients (12.1%) developed CIN [8].

These findings are in agreement with the results of our study, where, relatively higher proportion of cases with hypertension and those with mixed pathology had significantly higher incidence of CIN.

A total of 39.9% of those who underwent angiofigy, 32.7% with angioplasty, 26.3% with CT Brain and only 18.5% of those with CT KUB were reported to have CIN. The incidence of CIN is significantly higher among the cases with procedures such as Angiofigy, Angioplasty, CT brain, CT Abdomen/Pelvis contrast procedures (P-value<0.001).

AKI affects between 1% and 2% of the general population and up to 50% of high-risk subgroups following coronary angiofigy (CA) or percutaneous coronary intervention (PCI). CIN is often regarded in clinical practice as a transient event; in up to 80% of cases, Serum creatinine levels normalize after approximately 1–3 weeks [9-11].

After adjusting for comorbidities, both Levy and Mc Cullough *et al*. have demonstrated that in-hospital mortality is five times higher in patients who suffer CIN compared with patients receiving CM who do not, a 1-year mortality rates of between 20% and 38% [12, 13].

In a study conducted by Gruberg *et al*, as many as 20% of those developing CIN suffer persistent worsening renal function after CM exposure, with renal replacement therapy occurring in between 0.7% and 7% of patients with CIN [14].

A study conducted by Kane *et al* suggested that gadolinium was associated with a substantially lower incidence of deteriorating kidney function (5.3%) as compared to iodinated contrast (20.6%). Briguori C *et al* conducted a study in which in the gadolinium group, (28%) developed CIN and (6.5%) in the control group [15]. A study conducted by Nyman *et al*, reported that the dose of the iodinated CM was up to 10 times larger than that of the gadolinium chelates[16]. In addition, the gadolinium chelates were injected intravenously, while the iodinated CM were administered both intravenously and intra-arterially, with a higher concentration of the agent directly reaching the renal arteries.

In terms of mortality, in our study out of 1100 cases none died during their post-procedure stay at the hospital. As such CIN may be a marker of adverse cardiovascular outcomes rather than an independent risk factor. A recent meta-analysis by James *et al*, reviewed 39 observational studies that investigated cardiovascular outcomes in those with CIN and demonstrated an increased risk of mortality, cardiovascular events [17].

Pre-existent CKD is probably the most important pre-procedural risk factor for CIN risk becomes clinically significant when baseline serum creatinine concentration is ≥1.3 mg/dL in men and ≥1.0 mg/dL in women [18]. In our study also the group of CIN positive cases had higher pre-procedure mean serum creatinine and e-GFR levels than the group of CIN negative cases.

Procedural factors such as type, the total volume and previous CM exposure within 72 h are directly related to the development of CIN. In our study the incidence of CIN was relatively lower (though not statistically significant) with the Gadolinium than the Iso-Osmolar and Low-osmolar CM.

Limitation of the study

Thus, the differences in injected doses and injection sites, as well as the differences in molecular doses of administered iodinated CM and gadolinium chelates the former dose being more, may explain the higher reported nephrotoxicity of iodinated CM than of gadolinium chelates. Thus, the

comparative safety of iodinated versus gadolinium based CM is contradictory and enough evidence is not available to compare the safety between various types of iodinated CM and GBCA.

Conclusion

Amongst the various risk factors studied the patients with hypertension and a combination of two or more risk factors were observed to have higher incidence rates of CIN. Patients who underwent angiofigy, using iso-osmolar iodinated contrast media were observed to have statistically significant higher incidence rate of CIN.The use of Gadolinium based contrast media was found to have lower incidence of CIN, suggestive it to be a safer contrast media over iodinated contrast media

A significantly higher baseline pre and post-procedure serum creatinine and eGFR was observed in positive cases. In conclusion, although often a transient injury, CIN may progress to significant persistent renal impairment, ESRD (End stage Renal disease) and adverse cardiovascular outcomes. There are a number of recognized risk factors, although the prediction of CIN, particularly prior to contrast administration, remains challenging. The unmet clinical need in CIN therefore resides in accurate prediction, effective intervention and rapid detection to prevent adverse cardio renal outcomes. Each of these areas, particularly predictive risk scoring systems, innovative pharmacological and mechanical interventions and novel biomarkers are currently the subject of intensive research and development that may lead to the future development effective strategies to prevent the risk of CIN. In the present study, we found that the incidence of CIN was 27.3%. Our results showed that, the incidence of CIN was significantly higher in the older and obese adults. In addition, the existence of co-morbidity, the type of contrast procedure used was significantly associated with the increased incidence of CIN. We also found that the incidence of CIN was independent of sex and the type of contrast media used. The incidence of CIN did not differ significantly across the iodinated and gadolinium based CM used. However, relatively higher contrast media dose used was significantly associated with the increased incidence of CIN.

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