Incidence of Contrast Agent Induced Acute Kidney Injury and Analysis of Factors affecting it

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Abstract: *Contrast agents are widely used in many radiological investigations. Contrast induced acute kidney injury (CIAKI) is the third most common cause of hospital acquired renal insufficiency. The aims of this study were to assess the incidence of CIAKI and to analyse effects of various factors affecting CIAKI. The presence and severity of acute kidney injury was compared between a group of patients exposed to contrast agent to that in a group of patients not exposed to contrast agent. and the effect of various factors affecting it was noted. There was a statistically significant difference in the rise of S Cr in the exposed group as compared to the non exposed group. The incidence rate of CIAKI was 10.9%. Patients with low eGFR ($\leq$60 ml/min/1.73 m^2) had a 17.9 times chance of being affected by CIAKI as compared to patients with eGFR>60 ml/min/1.73m^2 and diabetics had a 7.6 times higher chance of getting affected by CIAKI as compared to non diabetics. Contrast administration can lead to rise in S Cr and thus acute kidney injury in a small but significant number of patients. Low eGFR and diabetes are associated with development of CIAKI.*

Keywords: Contrast induced acute kidney injury, CIN, Radiocontrast nephropathy, CECT, Diabetes, Chronic kidney disease

1. Introduction

A large number of radiological investigations need contrast administration to improve the visualization of different structures, i.e. to improve the 'contrast'. Iodinated contrast materials are one of the most commonly used contrast media. The contrast materials are not free of adverse effects, and are a cause of small but significant amount of morbidity and sometimes mortality

Adverse contrast reactions include pruritus, exanthema, vasculitis, cardiogenic shock, cardiac arrhythmia, cardiac arrest, headache, nausea, vomiting, hypotension, bronchospasm, tachycardia/bradycardia, wheezing, hypertension, dyspnea and pulmonary edema to respiratory arrest, angioedema, convulsions, profound hypotension and loss of consciousness.[1]

It is estimated that about 1, 50, 000 patients suffer from CIAKI per year in the world, and out of these, at least 1% require dialysis and a prolonged hospital stay.[2] With rising number of radiological investigations, CIAKI becomes an important adverse effect that should be studied in detail.

KDIGO (Kidney Disease Improving Global Outcomes) work group defines CIAKI as an acute kidney injury secondary to intravascular radiocontrast media exposure.[3]

The American College of Radiology has recommended using the AKIN criteria to define contrast-induced nephropathy.[4]

According to the ESUR (European society of urogenital radiology) guidelines for contrast media, the risk factors for contrast medium induced nephropathy are: [5]

Patient related
-eGFR less than 60 ml/min/1.73 m^2 before intra-arterial administration
-eGFR less than 45 ml/min/1.73 m^2 before intravenous administration
-In particular in combination with

Diabetic nephropathy
Dehydration
Congestive heart failure (NYHA grade 3-4) and low LVEF
Recent myocardial infarction (< 24 h)
Intra-aortic balloon pump
Peri-procedural hypotension
Low haematocrit level
Age over 70
Concurrent administration of nephrotoxic drugs known or suspected acute renal failure
And Procedure related
Intra-arterial administration of contrast medium
High osmolarity agents

Large doses of contrast medium
Multiple contrast medium administrations within a few days

CKD is the single most important predictor of CIAKI. Waybill MM et al. have shown that patients who have an estimated GFR< 60 ml/min per 1.73 m^2 are at an increased risk for development of AKI. The Consensus Guidelines for the Prevention of Contrast Induced Nephropathy considers those with eGFR<45 ml/min/1.73 m^2 to have a moderate risk for CIN.[6]

McCullough PA et al. concluded that in patients with renal impairment, diabetes mellitus amplifies the risk of CIAKI and complicates postprocedure management.[7]

The Consensus Guidelines for Prevention of Contrast Induced Nephropathy includes nephrotoxic drugs-loop diuretics, amphotericin B, aminoglycosides, vancomycin, NSAIDs, angiotensin converting enzyme inhibitors as a risk factor.[8]

Studies done by Rihal CS et al. and Dangas G et al. have lead to a conclusion that CCF and MI are independent risk factors for development of CIAKI.[9, 10]

Katzberg RW et al. compared few major studies addressing the question of whether the rates of CIAKI development were higher with intra-arterial or intravenous route and found that the ratio of rates of CIAKI developing after intra–arterial administration as compared to intravenous administration was 2.2 [11]

Apart from the risk factors mentioned above, the Consensus Guidelines for the Prevention of Contrast Induced Nephropathy also mentions sepsis or acute hypotension, dehydration or volume contraction, previous chemotherapy, history of organ transplant, vascular disease (hypertension, congestive heart disease, cardiac or peripheral vascular disease), infection with HIV or AIDS, collagen vascular disease and being a first nation person, to be risk factors for contrast induced nephropathy.[8]

Mehran R et al. have developed a risk score for calculation of incidence of CIAKI after PCI based on eight identified variables, i. e, hypotension, intra-aortic balloon pump, congestive heart failure, chronic kidney disease, diabetes, age >75 years, anemia, and volume of contrast. All these variables were assigned a weighted integer and the sum of the integers was a total risk score for each patient.[12]

2. Aims and Objectives

The Objectives of this study were to:
1) Assess the incidence of CIAKI in patients undergoing CECT and IVP and their comparison with patients undergoing NCCT.
2) Analyse the effect of eGFR, Diabetic nephropathy, CCF, history of recent MI, age, administration of nephrotoxic drugs, the type and the dose of the contrast medium used on CIAKI.

3. Materials and Methods

A set of 110 patients exposed to intravenous iodinated contrast agents and a set of matched 110 patients undergoing NCCT scans were studied.

Two values of serum creatinine prior to the study were taken and their average was used as a baseline creatinine value.

For CECT scans: Omnipaque300 (active ingredient: Iohexol, 300 mg I /ml) 100 ml IV was used and for IVP scans: Urografin 76% (active ingredients: sodium amidotrizoate, meglumineamidotrizoate, 370 mg I /ml), 40 ml IV was used. The post procedure creatinine value was taken after 48 hours of the study. CKD was defined as the presence of eGFR< 60 ml/min/1.73 m^2. eGFR was estimated using MDRD equation. Staging of CIAKI was done as follows according to the AKIN criteria.

Stage	Serum Creatinine value	Urine output
1	Serum creatinine increase ≥26.5 μmol/l (≥0.3 mg/dl) OR increase to 1.5–2.0-fold from baseline	<0.5 ml/kg/h for 6 hours
2	Serum creatinine increase >2.0–3.0-fold from baseline	<0.5 ml/kg/h for 12 hours
3	Serum creatinine increase >3.0-fold from baseline or serum creatinine ≥354 μmol/l (≥4.0 mg/dl) with an acute increase of at least 44 μmol/l (0.5 mg/dl) or need for RRT	<0.3 ml/kg/h for 24 h or anuria for 12 h OR needs for RRT

4. Observations

Out of the 110 patients in the exposed group, 90 underwent CECT and 20 underwent IVP. The groups were matched to a set of 110 non exposed patients on the basis of factors other than 'contrast administration', which are presumed to be associated with CIAKI

Table 1: Patient Characteristics of the two groups

Characteristics	Exposed (110 patients)	Non-Exposed (110 patients)	P value	Significance
Age (±SD) yrs	50.04±18.09	48.8±18.11	0.613	Not significant
Sex Distribution Female Male	50 60	54 56	0.685	Not significant
Diabetics	36 (32.7%)	33 (30%)	0.771	Not significant
Patients with eGFR<60 ml/min/1.73m^2 (CKD)	11	8	0.632	Not significant
Patients on nephrotoxic drugs	29	25	0.639	Not significant
Patients with a recent history of MI/CCF	8	8	1	Not significant

The p values for all the characteristics of the two groups are more than 0.05, implying that there is no statistically significant difference between the two groups.

68 out of 110 exposed patients (61.8%) were aged more than 60 years, and 74 out of 110 (67.2%) non exposed patients were aged more than 60 years.

50 out of 110 exposed patients (45.4%) were females and 60 (54.6%) were males, whereas 54 out of 110 (49%) non exposed patients were females and 56 (51%) were males.

74 out of 110 exposed patients (67.2%) were non diabetic and 36 (32.8%) were diabetic, whereas 77 out of 110 (70%) non exposed patients were non diabetic, and 33 (30%) were diabetic.

Out of the 110 exposed patients, 99 patients (90%) had eGFR>60 ml/min/1.73m^2, and 11 had eGFR<60 ml/min/1.73m$^{2.}$ Whereas out of 110 non exposed patients 102 (92.7%) had eGFR>60 ml/min/1.73m^2 and 8 had eGFR<60 ml/min/1.73m$^{2.}$

Table 2: Incidence of acute kidney injury in the two groups

Outcome	Exposed	Non exposed	Total
Acute Kidney injury present	12	3	15
Acute Kidney injury absent	98	107	205
Total	110	110	220

A total of 15 patients developed AKI as per the definition use in the present study. Twelve patients belonged to the Exposed group whereas three patients belonged to the Non Exposed group. The incidence rate of AKI in the exposed group was 10.9% whereas in the non exposed group was 2.72%. The risk ratio was 4. The population attributable fraction was 0.6. The p value between the two groups was 0.016. (<0.05, significant)

Table 3: Distribution of acute kidney injury in the two groups according to severity

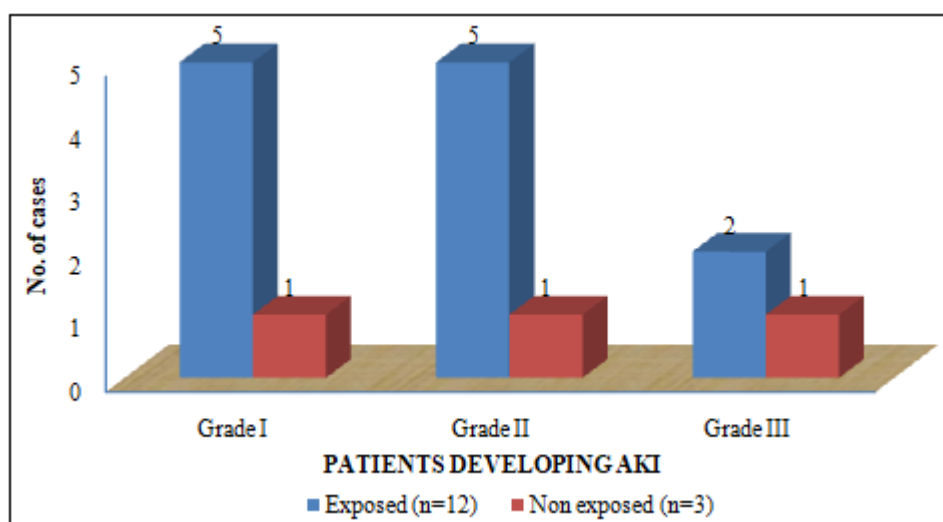| AKI grade	Exposed	Non exposed
Grade I	5/12 (41.6%)	1/3 (33%)
Grade II	5/12 (41.6%)	1/3 (33%)
Grade III	2/12 (16.6%)	1/3 (33%)

Figure 1: Grading distribution of acute Kidney Injury in the two groups

In the exposed group, a total of 12 patients developed acute kidney injury at 48 hrs. One of these was of grade I severity, and five each of grade II and III severity. In the non exposed group, a total of 3 patients developed acute kidney injury at 48 hrs. One patient each belonged to the three grades, i. e, grade I, II and III.

Overall, 11 patients (10%) out of the exposed group had eGFR<60 ml/min/1.73m^2. The incidence of CIAKI in these patients was 54.5% (6 patients). The incidence of CIAKI in rest of the patients was 6.06% (6 patients). The p value is 0.0002 (less than 0.05) which implies that the difference is statistically significant. The adjusted odds ratio (by logistic regression) was 17.915.
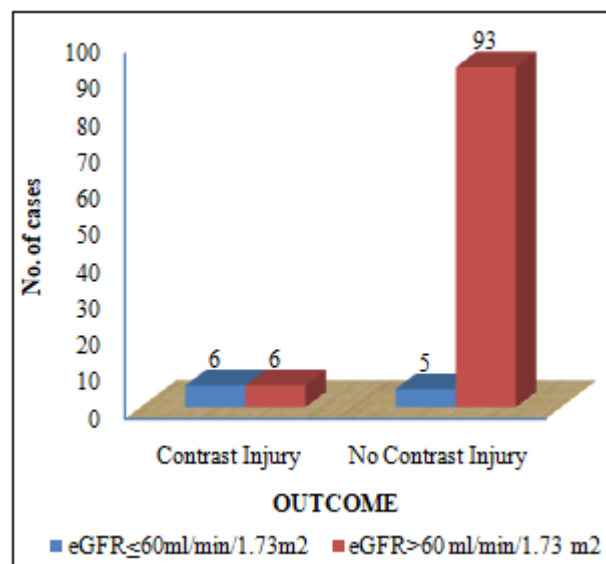

Figure 2: Contrast injury in patients with CKD (eGFR≤60ml/min/1.73 m^2) as compared to those without CKD

There were 36 diabetic patients in the exposed group. Out of these, 9 patients (25%) developed CIAKI and the incidence in the rest of the individuals was 4.05%. The p value is 0.002 (less than 0.05) which implies that the difference is statistically significant. The adjusted odds ratio (by logistic regression) was 7.613
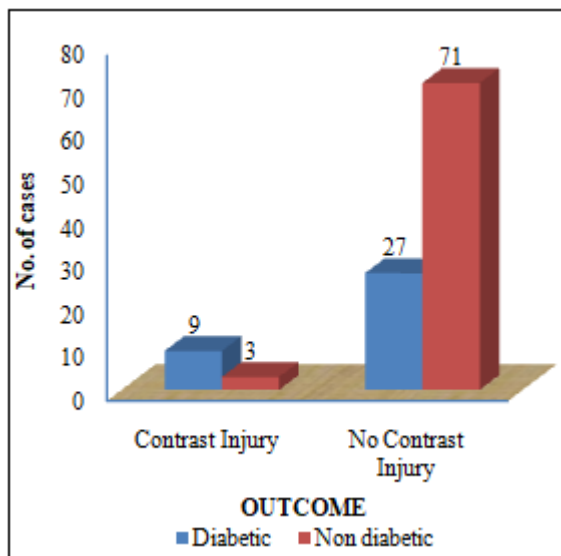

Figure 3: Contrast injury in diabetics as compared to non diabetics

Microalbuminuria was divided into 20-150 mcg/mg creatinine (low) and 151-300 mcg/mg creatinine (high). Out of the 36 diabetic patients, 18 (50%) had high levels of microalbuminuria and the rest had low levels of microalbuminuria. The p value is 0.443 (more than 0.05) which implies that the difference is not statistically significant.

42 patients (38.1%) out of the 110 patients exposed to contrast medium were aged more than 60 years. The incidence of CIAKI in the patients aged more than 60 years was 16.7%, and 7.3% in patients aged less than 60 years. The p value is 0.206 (more than 0.05) which implies that the difference is not statistically significant.

There were 50 females and 60 males in the exposed group. Out of the 50 females, 6 developed CIAKI (12%). Out of the 60 males, 6 developed CIAKI (10%). The p value is 0.767 (more than 0.05) which implies that the difference is not statistically significant.

Out of the 110 patients in the esposed group, 29 patients (26%) were consuming nephrotoxic drugs and out of these, 4 patients (13.8 %) developed CIAKI. Out of the 81 patients not consuming nephrotoxic drugs, 8 developed CIAKI. The p value is 0.729 (more than 0.05) which implies that the difference is not statistically significant.

8 patients (7.3%) out of 110 patients in the exposed group had a history of CCF/recent MI, and out of these, 2 developed CIAKI (25%). Out of the 102 patients with no recent history of CCF/MI, 10 developed CIAKI. The p value is 0.210 (more than 0.05) which implies that the difference is not statistically significant.

Out of the 110 patients of the exposed group, 90 patients had IV Iohexol (100 ml) as contrast agent and the rest 20 had IV Amidotrizoate (40 ml) as contrast agent.10 patients (11.1%) out of the 90 receiving Iohexol had CIAKI, and 2 out of the rest 20 patients with Amidotrizoate had CIAKI (10%). The p value is 1 (more than 0.05) which implies that the difference is not statistically significant.

5. Discussion

Table 4: Comparison of the present study with other similar studies

	Present Study	Mehran R et al. (12)	McCullough PA et al. (13)	Mitchell AM et al. (14)	Dangas G et al. (10)
Number of patients	220 (110+110)	5571	1826	633	7230
Patient profile	CECT, IVP and NCCT	Coronary intervention	Coronary intervention	CECT outpatient setting	Coronary intervention
Incidence of CIAKI	10.9%	13.1%	14.5%	11%	14.8%
Parameters associated with CIAKI	Baseline eGFR, Diabetes	chronic kidney disease, diabetes, congestive heart failure, age >75 years, hypotension, intra-aortic balloon pump, anemia, and volume of contrast	CrCl, diabetic status, and expected contrast dose for patients requiring dialysis	-	Decreased eGFR, Diabetes Periprocedural hypotension Higher contrast agent volume, low baseline hematocrit, Pulmonary edema at presentation, IABP use, LVEF<40%

In the present study, we found that acute kidney injury was significantly associated with contrast administered studies, with a risk ratio of 4 as compared with plain studies.

The incidence of contrast administered patients having CIAKI in our study was 10.9 %, which varies widely in different studies ranging from as low as 1% as shown in studies by Parfrey P et al.1[5] to as high as 19 % as shown in the study by Marenzi G et al.1[6] depending on various factors. Similar result as that of our study has been obtained

by Mitchell AM et al. on a study done in outpatient setting on patients undergoing CECT, who found the incidence of CIAKI to be 11%.1[4] Other major studies like that by Mehran R et al. and McCullough PA et al. have produced similar results with incidence rates of 13.1 % and 14.5% respectively.1[2, 13]

Low eGFR (<60 ml/min/1.73 m^2) was found to be significantly associated with the incidence of CIAKI and the adjusted odds ratio was 17.915. Rudnick MR et al. have

shown that low eGFR raised the risk of CIAKI by 20 times [17]. It has also been found to be an independent risk factor in studies done by McCullough PA et al., Mehran R et al. and Rihal CS et al.[9, 12, 13]

Diabetes was also significantly associated with CIAKI in our study, with an odds ratio of 7.613. Diabetes has been found to be an independent risk factor in a study by Mehran R et al.[12] Other studies done by Seeliger E et al.[18] and Lautin EM et al.[19] also highlight the importance of diabetes mellitus in the incidence of CIAKI.

In the present study, microalbuminuria was not found to be associated with CIAKI. This may be due to the fact that diabetic nephropathy can exist in non-proteinuric patients as well.

In the present study, no statistically significant difference was found to be associated with the type of contrast material used (ionic vs nonionic) in the incidence of CIAKI. Schwab SJ et al.[20] have reported similar findings. They found that creatinine levels increased by at least 0.5 mg/dL in 10.2% of the patients receiving diatrizoate, and 8.2% of the patients receiving Iopamidol, with p value not being significant.

In the present study, the incidence of CIAKI in patients ≥ 60 years was 16.7%, and 7.3% in patients aged less than 60 years. The difference was not statistically significant in this study, however, similar high rates with increasing age have been found in other studies. A Study by Marenzi G et al.[16] also reported age ≥ 70 years to be an independent predictor of CIN. Mehran R et al. also concluded age >75yrs to be an independent risk factor.[12]

A history of recent MI/ CCF was not significantly associated with the incidence of CIAKI in the present study, which may be explained by the fact that there were only a few patients with history of CCF/MI in our study (16/220). However, a few studies, like that done by Rihal CS et al., Marenzi G et al. and Dangas G et al. conclude that CCF is an independent risk factor.[9, 10, 16]

Nephrotoxic drugs were also not found to be significantly associated with CIAKI in the present study. Few studies, like that by Gleeson TG et al.[21] conclude that such drugs render the kidney more vulnerable to nephrotoxic contrast agents, however, their individual roles as independent risk factors of contrast-induced nephropathy is yet to be determined in large prospective clinical trials.

Our study suggests that multiple risk factors may predispose a patient more to CIAKI than the presence of a single factor. The cases with grade III CIAKI had multiple risk factors associated with them. Both the cases had an age of more than 60yrs, were diabetic and had low eGFR of 46.6 and 62ml/min/1.73m^2. Four out of the five cases with grade II CIAKI had an eGFR of ≤ 60 ml/min/1.73m^2, were diabetic and aged more than 60 yrs.

6. Conclusion

The salient findings of the present thesis work are:
- There is a statistically significant difference between the creatinine rise in contrast studies as compared to non contrast studies.
- The incidence of CIAKI was 10.9%
- Low eGFR (≤ 60 ml/min/1.73 m^2) and being a diabetic patient are significantly associated with the incidence of CIAKI.
- Patients with low eGFR (≤ 60 ml/min/1.73 m^2) had a 17.9 times chance of being affected by CIAKI as compared to patients with eGFR>60 ml/min/1.73m^2.
- Diabetics have a 7.6 times higher chance of getting affected by CIAKI as compared to non diabetics.
- Lower eGFR is also significantly associated with the degree of CIAKI.

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