ORIGINAL ARTICLE

Iso-osmolality and low-osmolality iodinated contrast medium during intravenous contrast-enhanced computed tomography: Effect on renal function

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Abstract

Background: Iodinated contrast media are well tolerated, and their use is popular. However, the most life-threatening side effect of iodinated contrast media is acute renal damage. *Aim and Objectives:* This study aimed to find the incidence of Contrast-Induced Acute Kidney Injury (CI-AKI) using Iso-Osmolar Contrast Media (IOCM) and Low-Osmolar Contrast Media (LOCM) in the general population. *Material and Methods:* This hospital-based observational study involved 40 subjects aged >18 years. An early increase in serum creatinine concentration of at least 0.5 mg/dl or a 25% increase in Serum Creatinine (SCr) from baseline were categorized as CI-AKI. The major outcome variable was SCr levels. The key explanatory variable was the intravenous contrast agent. For quantitative variables, mean ± SD were used, whereas, for categorical variables, frequency and proportion were used. *Results:* The IOCM group involved 37.50% and LOCM involved 62.50% subjects. The comorbidities recorded were diabetes in 17.50%, diabetes and hypertension in 15%, and hypertension in 12.50%. The mean baseline SCr amongst both the groups showed insignificant difference (p-0.527). There was an insignificant difference in the mean SCr between both the groups (p-0.302). The association between comorbidities and IV contrast agent was insignificant (p-0.412); the iodixanol group found a greater proportion (53.33%) compared to the iohexol group (40%). In the overall study population 92.50% had ≤ 1.4 and 7.50% had > 1.4 SCr levels implicating 7.50% incidence of Contrast-Induced Nephropathy (CIN). *Conclusion:* The results reveal iodixanol to have no risk of CIN however, iohexol had high incidence of CIN.

Keywords: Iso-osmolar contrast media, low osmolar iodinated contrast media, contrast-induced nephropathy, serum creatinine

Introduction

The use of Contrast Medium (CM) in interventional and diagnostic procedures is growing. As a consequence, CM exposure-related iatrogenic renal function impairment, sometimes referred to as Contrast-Induced Nephropathy (CIN), is more prevalent. An acute renal impairment following intravascular CM exposure that cannot be attributed to any other cause may be referred to as CIN. However, no widely accepted or applied standard definition is available in the literature [1]. The most frequent definition of CIN nowadays is a 25% rise in Serum Creatinine (SCr)

from the reference point, or an absolute rise of 0.5 mg/dL or higher, 48–72 hours after exposure to CM. Radiographic CM is the third common cause of renal failure following reduced renal perfusion and the use of nephrotoxic medications, accounting for 11% of cases of hospital-acquired renal inefficiency. Coronary angiography and Percutaneous Coronary Interventions (PCI) have the greater risks of CIN among all procedures that use CM for diagnostic or therapeutic purposes[2].

The diagnosis of CIN is based on a total or comparative rise in SCr, a temporal association between the increase in SCr and exposure to a contrast agent, and the exclusion of other possible causes of renal impairment [3]. The initial 24 hours post-exposure appear to be crucial in the development of CIN. A study indicated that 80% of CIN cases showed a trajectory of SCr elevation [4]. The majority of iodinated CM Adverse Events (AEs), such as nausea, vomiting, urticaria and itching are minor. Severe AEs, such as hypotensive shock, respiratory arrest, cardiac arrest and convulsions can occur. After switching from iso-osmolar CM (IOCM) to low-osmolar CM (LOCM), the incidence of these AEs has fallen significantly. For IOCM, the incidence of AEs has been reported to be 5% to 15%, and for LOCM, 0.2% to 0.7% [5]. Patients with normal baseline renal function have a 2% chance of developing CIN, while those with a reference point SCr >2 mg/dL had a 20% to 30% chance [6]. Clinical history, physical examination, and basic laboratory testing can reveal the majority of CIN risk factors. The most important pre-procedural risk factor for CIN is pre-existing chronic renal disease, because a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 is a major risk factor for CIN. Diabetes Mellitus (DM), volume depletion, nephrotoxic medication usage, hypotension, age >75 years, advanced heart failure, left ventricular systolic function <45%, and anemia are all independent predictors of CIN [7-8].

Despite significant advances in improving the quality of CM, medics continue to be concerned about acute kidney impairment following intravascular contrast injection. Contrast-Induced Acute Kidney Damage (CI-AKI) is a serious complication of using an iodine CM for diagnostic or interventional procedures [9]. Whether different forms of contrast media with varied osmolarities are associated with a decreased incidence of CI-AKI remains unresolved [6].

There have been conflicting results regarding whether IOCM is associated with a lower risk of CI-AKI compared to LOCM. The European Society of Urogenital Radiology and Kidney Disease: Improving Global Outcomes guidelines has suggested both LOCM and IOCM in subjects with greater risk of CI-AKI [11-12]. Diabetic nephropathy, a kidney complication arising from DM, is a significant contributor to Chronic Kidney Disease (CKD) and a major public health concern in the 21st century. In individuals with CKD, especially when DM co-occurs, the risk of CI-AKI is dramatically increased. The nephrotoxicity has been assessed across LOCM and IOCM, especially in subjects with diabetes, by numerous studies. However, whether there are any substantial changes in renal safety between IOCM and LOCM is still unknown. In this context, we evaluated the effect of intravenous (IV) Contrast-Enhanced Computed Tomography (CECT) with IOCM and LOCM on kidney function [7].

Material and Methods

This observational study was conducted in the Department of Radiodiagnosis at Jawaharlal Nehru Medical College KAHER University, Belagavi, India. All the eligible patients (> 18 years) undergoing CECT requiring IV CM were considered as the study population.

Sampling Technique: A universal sampling technique was employed for the study. As per Moos *et al*. (2013), the rise in SCr > 25% of baseline was 4.96%m and the other parameters considered for the sample size were precision of 7% and a 95% confidence interval [8]. Sample size was calculated using the formula n=4pq/d2**,** Where p: the prevalence of subjects who developed an elevation in SCr >25% of baseline (6.5%), q: 1 – p, d: absolute precision of 7 as per McDonald *et al*. (2013) [9]. According to the formula, the required sample size was 38. After accounting for a 5% loss to follow-up, 2 additional cases were included, bringing the total number of subjects considered for the final study to 40.

Data were collected over the course of one year using the universal sampling method.Those with a known allergy to contrast media, any absolute contraindication to its use, or patients clinically advised against undergoing CECT due to impaired kidney function were excluded. Ethical approval was obtained, and participants were informed about the study's risks and benefits, as well as the voluntary nature of participation. Written informed consent was collected, and participant confidentiality was maintained throughout the study. Data were recorded using a structured proforma. All patients underwent clinical evaluation, and CECT was performed using a GE Evolution 128-slice CT scanner. The CT protocol included scout images, plain images, and contrast-enhanced images. SCr levels were measured 48–96 hours post-CECT, based on the observation that SCr typically rises 2 to 5 days after contrast exposure.

Statistical analysis

For quantitative variables, data were summarized as mean ± Standard Deviation (SD) when normally distributed, and as median with Interquartile Range (IQR) when non-normally distributed. Categorical variables were summarized using frequency and proportion (%). The Shapiro–Wilk test was used to assess the normality of quantitative data, with a p-value > 0.05 indicating a normal distribution. To compare baseline renal function parameters (such as serum creatinine and eGFR) between the two independent groups those receiving iso-osmolality contrast medium and those receiving low-osmolality contrast medium an independent samples t-test was used for normally distributed variables. To evaluate the within-group change in renal function (i.e., pre- and post-contrast exposure), a paired t-test was applied for normally distributed variables measured at two time points (before and 48–72 hours after contrast administration). This allowed for assessment of the effect of contrast media on renal function over time within each group. A p-value < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0.

Results

In the study population (40 subjects), male and female participants were 25 (62.50%) and 15 (37.50%) respectively. The participants were aged between 19 to 85 years with the mean age 53.85 ± 17.17 years. Amongst them 5 (12.50%) were aged

up to 30 years, 7 (17.50%) were aged between 31-45 years, 15 (37.50%) were aged between 46 - 60 years, and 13 (32.50%) participants were > 60 years. While 22.50% participants had undergone CECT of abdomen and pelvis, 10% participants underwent CECT brain. Iodixanol and iohexol were administered to 37.50% and 62.50% of participants, respectively.

Table 1. The renal function of the study participants was assessed using both SCr levels and creatinine clearance values before and after contrast administration (at 48–96 hours post-procedure). The mean baseline SCr was 1.03 ± 0.28 mg/dL, with a median of 1.00 mg/dL, ranging from 0.50 to 1.80 mg/dL. After 48–96 hours of contrast exposure, the mean SCr remained unchanged at 1.03 ± 0.28 mg/dL, with the same median and range, indicating no significant change in mean SCr values post-contrast.

Similarly, analysis of creatinine clearance values showed that the mean baseline SCr clearance was 83.17 ± 33.62 mL/min, with a median of 81.25 mL/min, ranging from 34.10 to 183.30 mL/min. At 48–96 hours post-contrast, the mean SCr clearance was 83.11 ± 33.54 mL/min, with a median of 80.95 mL/min, and a range of 34.20 to 183.30 mL/min.

These findings indicate that there was no clinically or statistically significant change in either SCr levels or creatinine clearance values following CECT imaging. This suggests a low risk of CIN in the studied population under the given conditions.

The observations of outcomes of contrast agents on SCr is presented in Table 2. The mean baseline of SCr was 1.07 ± 0.33 and 1.01 ± 0.25 mg/dL in iodixanol and iohexol group, respectively. The difference between the two groups was statistically insignificant ($p = 0.527$). The mean of SCr after 48 - 96 hours was 1.09 ± 0.33 and 1 ± 0.25 mg /dL in iodixanol and iohexol group respectively. The difference between the two groups was statistically insignificant ($p = 0.302$).

Table 1: Descriptive analysis of serum creatinine levels

Parameter	Mean ± SD	Median	Min	Max
Baseline SCr*	1.03 ± 0.28	1.00	0.50	1.80
SCr after 48-96 hours*	1.03 ± 0.28	1.00	0.50	1.80
Baseline SCr clearance**	83.17 ± 33.62	81.25	34.10	183.30
SCr clearance after 48-96 hours**	83.11 ± 33.54	80.95	34.20	183.30

*mg/dL; ** mL/min; SCr – Serum creatinine*

The intra group comparison of mean SCr in pre-operative and after 48 to 96 hours revealed, among the iodixanol group, the mean SCr of baseline and after 48 to 96 hours was 1.07 ± 0.33 and 1.09 ± 0.33 mg/dL respectively, which was found to be significant (p-0.301). Similarly, among the iohexol group, the mean SCr of baseline and after 48 to 96 hours was1.01 ± 0.25 and 1.00 ± 0.25 mg/dL respectively, which was found to be insignificant (p = 0.722). In iodixanol and iohexol group, the median SCr change was 0 (IQR 0 to 10) and 0 (IQR 10 to 10.56) respectively. The difference in the SCr change between the groups

was insignificant (*p*-0.525). (Table 3) Among patients with high baseline Scr (>1.4 mg/dL), 25% (2 out of 8) of those who received iodixanol showed a rise in SCr, compared to 10% (1 out of 10) in the iohexol group. Conversely, among those with normal or low baseline creatinine (≤ 1.4 mg/dL), 75% (6 out of 8) in the iodixanol group and 90% (9 out of 10) in the iohexol group exhibited post-contrast creatinine elevation. Among the study population, 7 (17.50%) participants had diabetes, 6 (15%) participants had diabetes and hypertension, and 5 (12.50%) participants had hypertension. The baseline SCr range among population with co-morbidity revealed that (n = 18), 3 participants had high (> 1.4 mg/dL) and 15 participants had low (≤ 1.4 mg/dL) SCr levels (Table

Table 2: Comparative analysis of serum creatinine between intravenous contrast agents

Parameter	IV contrast agent		p
	Iodixanol†	Iohexol††	
Baseline Scr*	1.07±0.33	1.01±0.25	0.527
SCr after 48-96 hour*	1.09±0.33	1±0.25	0.302

mg/dL; †n=15; ††n=25; SCr – Serum creatinine

Table 3: Analysis of baseline creatinine range amongst population with co-morbidities

Baseline creatinine	Iodixanol†	Iohexol††	p
High (>1.4)	2 (25%)	1 (10%)	0.559
Low (<=1.4)	6 (75%)	9 (90%)	

†n=8; ††n=10

Table 4: Comparative analysis of contrast-induced nephropathy of intravenous contrast agents

CIN	Iodixanol†	Iohexol††	p
Positive (> 0.5)	0	3	*
Negative	15	22	--

*†n=15; ††n=25; * No statistical analysis performed; CIN – Contrast induced nephropathy*

3). Out of the 40 study participants, 7.50% were positive (SCr >1.4 mg/dL) and 92.5% were negative (SCr ≤ 1.4 mg/dL) to CIN (Table 4).

Discussion

Numerous observational studies have subsequently examined how often AKI occurs after the intra-arterial and intravenous use of CM, and the vast majority of these studies identified a notable risk [10]. CIN is a major concern among the general population and particularly in subjects with comorbidities, especially when iodinated CM is used [11]. There is still a debate on whether certain CM types with different osmolarities are linked to a lower incidence of CI-AKI. Despite significant advances in improving the quality of CM, clinicians continue to be concerned about AKI following intravascular contrast injection [12]. Our study revealed that, iodixanol outperforms iohexol in terms of reducing the risk of CIN. A study by Nguyen *et al*. found the baseline SCr in the iodixanol group had decreased on first day, however, the change was insignificant on third day [13]. In the iopromide group (low-osmolality), there was an increase in SCr on first and third day, our observations yielded similar findings. We observed that, the association of gender and IV contrast agents across the groups was insignificant and displayed male predominance in both the groups. Although the relation between comorbidities and IV contrast agent was insignificant, the iodixanol group found a greater proportion as compared to the iohexol group. A univariate analysis by Sonhaye *et al*. observed that renal failure, diabetes, age >55 years, and IV contrast doses >150 mL were all risk factors for CIN [14]. Similar findings were reported by Colling *et al*. [15], and the previous study indicated that diabetes was the only factor independently linked to an increased risk of CIN in the multivariate analysis. However, these studies established the correlations in CM with low osmolarity non-ionic form. In the overall study group, 92.50% had SCr levels of ≤1.4, while the remainder had levels >1.4. The variation in IV contrast agents concerning baseline SCr was deemed insignificant. A meta-analysis by Zhoa *et al*. involving 15 RCTs with 2190 patients assessed the impact of IOCM versus LOCM on the prevalence of CI-AKI in diabetic patients [16]. They found that IOCM offered no significant advantage over LOCM in preventing CI-AKI in diabetic individuals, regardless of CKD status [17]. The total incidence of CIN was 7.50%. Among the 25 subjects using the iohexol IV contrast agent, 12% tested positive for CIN. Reed *et al*. found that iodixanol had a lower incidence of CI-AKI compared to iohexol or ioxaglate when IOCM was compared to iopromide, iopamidol, iomeprol, or ioversol [18]. However, similar outcomes were not observed when IOCM was compared to iopromide or iopamidol. In a prospective study by Rudnick *et al*. involving 299 patients, the incidence of CIN was 21.8% and 23.8% for iodixanol and ioversol, respectively [19]. Another meta-analysis by Eng *et al*. indicated that iodixanol slightly reduced the risk of CIN compared to a varied group of LOCM, though this was barely statistically significant [20]. A meta-analysis of 12 RCTs comparing IOCM with LOCM in assessing CIN occurrence in DM subjects revealed that iodixanol was not superior to LOCM in reducing CIN risk [21]. If CIN is defined as a relative increase in SCr of at least 25% from baseline, iodixanol showed a lower CIN incidence, which

was not significant; iodixanol was more effective than iohexol in reducing CIN risk; however, the difference between iodixanol and other non-iohexol LOCMs was not clear. Our research produced similar findings [22].

Conclusion

The study compared CI-AKI incidence between IOCM and LOCM in the general population. Overall CI-AKI incidence was low (7.5%). No statistically significant difference in SCr changes was found between iodixanol (IOCM) and iohexol (LOCM) groups. Iodixanol group had more patients with comorbidities and elevated baseline creatinine. Among CI-AKI cases, 12% were in the iohexol group versus 0% in the iodixanol group. Results suggest a potential slight advantage of iodixanol in reducing CI-AKI risk, especially in high-risk patients.

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