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Research Article

The Comparison of the Incidence Rate of Contrast-Induced Nephropathy with Iodixanol, Iohexol, and Iopromide Following Coronary Angiography

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Abstract

Purpose: The purpose of this study was to compare the incidence of contrast-induced nephropathy (CIN) with the three commonly used contrast media in coronary angiography.

Methods: In this prospective observational study, 574 consecutive patients who were referred for coronary angiography to our cardiovascular center, were included. Patients were categorized into three groups based on the received contrast media, including iopromide (Ultravist®), iodixanol (Visipaque®), and iohexol (Omnipaque®). Patients' demographic characteristics, past medical history, and risk factors were recorded. Renal function was evaluated in all the patients within 48 hours before and 72 hours after the procedure. CIN was defined as an increase in the serum creatinine level by 0.5mg/dl or by 0.25% from the baseline.

Results: Our results demonstrated that CIN occurred similarly in the 3 groups of contrast media (p-value = 0.935). Moreover, multivariate analysis revealed significant adjusted associations between CIN and smoking (OR: 2.832, 95% CI: 1.098-7.303, P: 0.031), pre-existing renal disease (OR: 8.252, 95% CI: 3.145-21.654, P < 0.001) and volume of contrast media (OR:1.004, 95% CI:1.001-1.008, P:0.024).

Conclusion: The three commonly used contrast media, iopromide, iohexol, and iodixanol have a similar risk of CIN in patients undergoing coronary angiography with or without PCI.

Keywords: Contrast Media; Coronary Angiography; Contrast-Induced Nephropathy; Iopromide; Iodixanol; Iohexol

Introduction

Radiographic contrast agents have been in use for over 60 years. An average contrast-enhanced CT uses about 40 grams of iodine chemically bound to an organic molecule that is injected directly into the vascular system. This is a very large dose of foreign material and speaks to the overall safety of these agents.

Iodinated X-ray contrast media are the most commonly used drugs in diagnostic and interventional procedures. Procedures that employ contrast media have shown rapid growth. In the last two decades, the use of CT has increased up to 8 times and cardiac catheterizations have increased by 3.9 times [1,2] Nonionic, iodinated contrast agents have long been used because they are believed to be safer than ionic, high-osmolality agents; however, they are also more expensive. These agents play an important role in diagnostic and interventional procedures, particularly cardiac angiography [3,4].

Despite the improvements in the chemical structure of the contrast media, Contrast-Induced Nephropathy (CIN) is still the third leading cause of hospital-acquired acute renal failure [5]. Given the increasing incidence of heart diseases and the subsequent increase in angiography that uses contrast media, it is essential to study ways to reduce the side effects of these materials and medical costs incurred on patients in this method. Like any other medication, contrast media also have adverse side effects, which impose very high medical costs on patients. Side-effects of these medications are categorized into allergic and non-allergic groups. The allergic side-effects occur minutes after injection, while non-allergic side-effects usually present hours to days after injection and include hemodynamic and systemic effects, coronary effects, renal effects, venous thrombosis, the effect on red blood cells, histamine release, changes in blood pressure, vagal reaction, and sudden epileptic attacks.

Classification of contrast agents and frequency of acute adverse events

Iodine-based contrast agents can be divided according to osmolarity (high, low, or iso-), ionicity (ionic or nonionic), and the number of benzene rings (monomer or dimer) [6]. Nonionic contrast agents cause less discomfort and fewer adverse reactions compared with ionic agents [6]. In current practice, nonionic low or iso-osmolar preparations are used almost exclusively for intravascular injections; and high-osmolar ionic agents are not discussed in this article. Iso- and low-osmolar contrast agents are associated with significantly lower rates of acute reactions compared with high-osmolar agents. The rate of acute adverse events for low-osmolar contrast agents is approximately 0.2%–0.7% [7-9] and for severe acute reactions, 0.04% [3] Fatal reactions to contrast media are rare, with an incidence of one in 170,000 injections [3] In general, clinical studies have not shown a significant difference in pharmacokinetics, pharmacodynamics, general safety, induction of thrombosis, and diagnostic effect among nonionic agents [10]. Both low osmolar and iso-osmolar agents have shown a low rate of CIN in the previous literature [11]. Since there is still controversy regarding the relative nephrotoxicity of these agents, we conducted this study to compare the risk of CIN with these agents after coronary angiography in a large patient population.

Methods

Study population

This prospective study included patients who were referred to our tertiary cardiovascular center for coronary angiography with or without percutaneous coronary intervention (PCI) from August 2019 to August 2021. The study protocol was approved by the research board and ethics committee of our center.

Study design and endpoint

This study was conducted as a prospective observational cohort study. The exposure considered the type of contrast media agent and the main outcome was the occurrence of CIN, defined as an increase in the absolute serum creatinine level by 0.5mg/dl or by 0.25% from the baseline. All the patients had a baseline laboratory evaluation including the serum creatinine level within 48 hours before the procedure. To evaluate for CIN, the evaluation of serum creatinine level and urine analysis were performed within 72 hours after the procedure. Also, a 30-day follow-up was performed in all the patients by telephone interviews regarding other complications and, if affected by CIN, the serum creatinine level in their following laboratory tests.

Contrast Media Agents

Three contrast media agents were applied for angiography in this study: iopromide (Ultravist®), iodixanol (Visipaque®), or iohexol (Omnipaque®).

Statistical analysis

IBM SPSS Statistics 20 for Windows (IBM Inc., Armonk, NY) was applied for statistical analysis. The fitness of interval variables to normal distribution was assessed by a one-sample Kolmogorov-Smirnov test. Data were described as median (interquartile range [IQR]) for interval and count (%) for categorical variables. Comparison among the groups was performed by Kruskal-Wallis test for interval and chi-square (or Fisher's exact) test for categorical data. Multivariable analysis was performed by using logistic regression models with a backward elimination method. P-value < 0.05 was considered statistically significant.

Results

Baseline, cardiovascular and medication history

Totally, 574 executive patients were included in the study. Patients' baseline data are presented in table 1. According to table 1, the patients in the three CM groups had relatively similar characteristics. However, the patients who received iopromide were more afflicted by hyperthyroidism and hyperlipidemia. On the other hand, patients in the iohexol group had less hyperlipidemia and less family history of cardiovascular diseases.

	Contrast Media Agent			P-value
	Iopromide (n = 132)	Iodixanol (n = 305)	Iohexol (n = 137)	
Female	56 (42.7%)	56 (42.7%)	56 (42.7%)	0.493
Age (years)	56 (48 - 65.25)	58 (51 - 66)	58 (50 - 66.5)	0.553
Weight (Kg)	77 (67 - 85)	72.5 (65 - 80)	73 (65 - 81.25)	0.026
Height (cm)	165 (156 - 172)	165 (158 - 171)	166 (159.75 - 172)	0.673
BMI	28 (25 - 31.3)	26.7 (24 - 30)	26 (24 - 30)	0.006
BSA (m^2)	1.87 (1.7 - 2)	1.83 (1.7 - 1.9)	1.83 (1.69 - 1.94)	0.161
Smoking	43 (33.6%)	104 (35.4%)	49 (37.7%)	0.787
Alcohol	14 (11%)	32 (11%)	13 (10%)	0.947
Atypical Chest Pain	17 (12.9%)	30 (9.8%)	14 (10.2%)	0.628
Typical Chest Pain	78 (59.1%)	184 (60.3%)	80 (58.4%)	0.921
Diabetes	37 (28%)	79 (25.9%)	36 (26.3%)	0.897
Asthma	8 (6.1%)	20 (6.6%)	12 (8.8%)	0.63
Smoking	43 (33.6%)	104 (35.4%)	49 (37.7%)	0.787
Kidney Disease	23 (17.7%)	54 (17.8%)	26 (19%)	0.947
Hypothyroidism	6 (4.6%)	18 (5.9%)	10 (7.3%)	0.643
Hyperthyroidism	7 (5.3%)	2 (0.7%)	1 (0.7%)	0.002
Seizure	3 (2.3%)	5 (1.6%)	3 (2.2%)	0.872
Previous Surgery	56 (42.7%)	124 (40.8%)	60 (43.8%)	0.821
Allergy to contrast	41 (31.1%)	78 (25.6%)	47 (34.3%)	0.143
Other Allergies	20 (15.2%)	40 (13.1%)	21 (15.3%)	0.765
Hyperlipidemia	67 (50.8%)	134 (43.9%)	49 (35.8%)	0.045
Anemia	31 (23.5%)	67 (22%)	23 (16.8%)	0.346
Family History				
CVD	58 (43.9%)	120 (39.3%)	41 (30.6%)	0.071
Hypertension	51 (38.6%)	109 (35.7%)	37 (27.6%)	0.134
Renal Diseases	16 (12.1%)	25 (8.2%)	12 (9%)	0.426

Table 1: Background characteristics of the patients.

Data presented as count (%) or median (IQR).

BMI: Body Mass Index; BSA: Body Surface Area; CM: Contrast Media Agent; CVD: Cardiovascular Disease

Cardiovascular findings are compared among the groups in table 2. The relative frequency of patients who underwent coronary angiography using iopromide was more than the other two agents (about 44%). Coronary artery disease severity was higher in the iodixanol group. Also, significant stenosis of LAD and RCA was seen in the iodixanol group more than in the two other groups. Heart failure was also more prevalent in these patients. The statistically significant difference in systolic and diastolic blood pressures was not clinically significant. All the medications used for the patients' treatment are presented in table 3. Patients in the iopromide group received more enoxaparin and nitroglycerine ($p < 0.05$).

	Contrast Media Agent			P value
	Iopromide (n = 132)	Iodixanol (n = 305)	Iohexol (n = 137)	
History				
Unstable Angina/ NSTE MI	37 (28.2%)	82 (26.9%)	31 (22.6%)	0.532
Stable Angina	48 (36.4%)	78 (25.6%)	26 (19%)	0.005
STEMI	48 (36.4%)	78 (25.6%)	26 (19%)	0.921
Hypertension	71 (53.8%)	154 (50.7%)	64 (46.7%)	0.507
Hypotension	9 (6.8%)	14 (4.6%)	7 (5.1%)	0.633
Dyspnea	31 (23.5%)	69 (22.6%)	25 (18.2%)	0.508
Exertional dyspnea	53 (40.2%)	125 (41%)	48 (35%)	0.486
PND	0 (0%)	5 (1.6%)	2 (1.5%)	0.556
Heart rate	78 (70 - 88.75)	78 (70 - 88)	77 (70 - 84.5)	0.559
Systolic blood pressure	130 (120 - 150)	130 (120 - 150)	140 (125 - 160)	0.030
Diastolic blood pressure	70 (69.25 - 80)	80 (70 - 80)	77 (70 - 80)	0.033
Ejection fraction (%)	45 (40 - 50)	45 (35 - 50)	45 (35 - 50)	0.839
Known CAD	105 (79.5%)	253 (83%)	112 (81.8%)	0.691
CAD Severity (vessels)				0.044
0	54 (40.9%)	118 (38.7%)	60 (43.8%)	
1	22 (16.7%)	44 (14.4%)	32 (23.4%)	
2	34 (25.8%)	67 (22%)	20 (14.6%)	
3	22 (16.7%)	76 (24.9%)	25 (18.2%)	
Significant Stenosis				
LAD	53 (40.5%)	150 (49.2%)	57 (41.6%)	0.146
RCA	48 (36.9%)	123 (40.5%)	40 (29.2%)	0.076
LCx	46 (35.4%)	117 (38.5%)	40 (29.2%)	0.17
Angioplasty	58 (43.9%)	99 (32.6%)	47 (34.3%)	0.07
Heart Failure	22 (16.7%)	61 (20.1%)	15 (10.9%)	0.06
NYHA Function Class				0.36
	1 (4.8%)	4 (6.6%)	1 (7.1%)	
	11 (52.4%)	44 (72.1%)	10 (71.4%)	
	8 (38.1%)	13 (21.3%)	3 (21.4%)	
	1 (4.8%)	0 (0%)	0 (0%)	

Table 2: Cardiovascular Problems among the patients.

Data presented as count (%) or median (IQR).

PND: Paroxysmal Nocturnal Dyspnea; CAD: Coronary Artery Disease; LAD: Left Anterior Descending Artery; RCA: Right Coronary Artery; LCX: Left Circumflex Artery

	Contrast Media Agent			P value
	Iopromide (n = 132)	Iodixanol (n = 305)	Iohexol (n = 137)	
Pethidine	7 (5.3%)	16 (5.2%)	9 (6.6%)	0.844
Agrastat	0 (0%)	1 (0.3%)	1 (0.7%)	0.718
Enoxaparin	6 (4.5%)	1 (0.3%)	0 (0%)	0.001
Adenosine	0 (0%)	4 (1.3%)	2 (1.5%)	0.557
Morphine sulphate	2 (1.5%)	7 (2.3%)	0 (0%)	0.187
Atropine	11 (8.3%)	17 (5.6%)	9 (6.6%)	0.528
Hydrocortisone	4 (3%)	2 (0.7%)	2 (1.5%)	0.11
Morphine	0 (0%)	2 (0.7%)	3 (2.2%)	0.174
Keflin	6 (4.5%)	11 (3.6%)	4 (2.9%)	0.776
Plasil	5 (3.8%)	7 (2.3%)	2 (1.5%)	0.552
TNG	21 (15.9%)	24 (7.9%)	10 (7.4%)	0.02
Lasix	0 (0%)	2 (0.7%)	0 (0%)	> 0.999
Contrast volume	150 (100 - 300)	150 (100 - 250)	150 (100 - 250)	0.100

Table 3: Prescribed medications among the patients.

Pre- and post-procedural laboratory findings

Table 4 demonstrates the routine pre- and post-procedural laboratory results in the study groups demonstrated by numbers 1 and 2, respectively. Although there were statistically significant differences between the groups regarding some parameters, these differences were not clinically significant making the groups comparable in this regard.

	Contrast Media Agent			P value
	Iopromide (n = 132)	Iodixanol (n = 305)	Iohexol (n = 137)	
Hemoglobin(g/dl)	13.8 (12.4 - 15)	13.8 (12.7 - 14.8)	13.75 (12.775 - 14.8)	0.893
PT (s)	13.8 (13.2 - 14.7)	13.9 (13.2 - 14.775)	13.45 (12.925 - 14.7)	0.036
PTT(s)	30 (28 - 31.925)	30 (28 - 32.525)	30 (29 - 32)	0.628
INR	1.1 (1.06 - 1.25)	1.2 (1.07 - 1.25)	1.1 (1.05 - 1.22)	0.063
Na1(mEq/L)	140 (139 - 142)	139 (137 - 142)	140 (137 - 142)	0.028
Na2(mEq/L)	140 (138 - 142)	139 (137 - 141)	140 (137 - 142)	0.007
K1(mEq/L)	4.1 (3.9 - 4.4)	4 (3.8 - 4.3)	4.2 (3.9 - 4.4)	0.004
K2(mEq/L)	4.2 (4 - 4.4)	4.1 (3.9 - 4.4)	4.2 (4 - 4.3)	0.610
Cr1(mg/dl)	1 (0.8 - 1.2)	0.9 (0.7 - 1)	0.8 (0.7 - 1)	0.011
Cr2(mg/dl)	1 (0.7 - 1.2)	0.9 (0.7 - 1.1)	0.86 (0.7 - 1)	0.042
BUN1(mg/dl)	16 (13 - 21)	16 (13 - 20)	16.3 (14 - 20)	0.449
BUN2(mg/dl)	15 (12 - 19)	16 (12 - 20)	17 (13 - 21.95)	0.089

Table 4: Laboratory findings among the patients.

Contrast-induced nephropathy

24 patients out of the 574 participants were afflicted by CIN, which proposed a cumulative incident of 4% after 72 hours. None of these patients required dialysis. As shown in table 5, the occurrence of CIN was not significantly different among the three contrast agents (p-value = 0.935). The 30-day follow-up of the patients revealed that in all the patients with CIN, the serum creatinine level had returned to baseline in the following days.

	Contrast-Induced Nephropathy		P-value
	Yes (n = 24)	No (n = 550)	
Age (years)	63 (56-68)	57 (50-67)	0.121
Female	6 (25%)	219 (39.8%)	0.146
BMI	26 (23-29)	27 (24-30)	0.298
Smoking	15 (62.5%)	186 (33.8%)	0.008
Atypical Chest Pain	2 (8.3%)	60 (10.9%)	0.691
Diabetes	8 (33.3%)	142 (25.8%)	0.416
Ejection fraction (%)	45 (35-50)	45 (40-50)	0.761
Heart Failure	5 (20.8%)	94 (17.1%)	0.633
Renal Diseases	12 (50%)	91 (16.5%)	< 0.001
Unstable Angina/ UNSTE MI	7 (29.2%)	145 (26.4%)	0.755
Hypertension	17 (70.8%)	273 (49.6%)	0.042
Hyper-sensitivity	3 (12.5%)	78 (14.2%)	0.812
Hyperlipidemia	10 (41.7%)	243 (44.2%)	0.808
Angioplasty	12 (50%)	191 (34.7%)	0.128
Adenosine	1 (4.2%)	5 (0.9%)	0.129
Metoclopramide	2 (8.3%)	11 (2%)	0.044
TNG	4 (16.7%)	50 (9.1%)	0.215
Lasix	0 (0%)	2 (0.4%)	0.917
Contrast Media Agent			0.935
iopromide	6 (25%)	126 (22.9%)	
Iodixanol	13 (54.2%)	293 (53.3%)	
Iohexol	5 (20.8%)	131 (23.8%)	
NYHA Function Class			0.013
I	16 (66.7%)	31 (5.6%)	
II	14 (58.3%)	373 (67.8%)	
III	0 (0%)	147 (26.7%)	
IV	5 (20.8%)	0 (0%)	
Baseline BUN	17.5 (15-24)	16 (13-20)	0.047
Baseline Cr	0.75 (0.60-1.15)	0.9 (0.7-1.1)	0.166
Contrast volume (cc)	250 (150-350)	150 (100-250)	0.026

Table 5: Association of the contrast-induced nephropathy with several predictors

Data presented as count (%) or median (IQR).

BMI: Body Mass Index; MI: Myocardial Infarction

The associations between the occurrence of CIN and patients' predisposing factors were assessed statistically and the results are presented in Table 5. Apparent relations can be observed between the CIN and smoking, background renal diseases, presence of hypertension, baseline BUN, the volume of contrast media, and patients' function class (p-value < 0.05 for all).

Multivariable analysis was performed to investigate the adjusted associations between the incidence of CIN and the above-mentioned predictors. The final results proposed significant adjusted associations between CIN and smoking (OR: 2.832, 95% CI: 1.098-7.303, P: 0.031), pre-existing renal disease (OR: 8.252, 95% CI: 3.145-21.654, P < 0.001) and volume of CM (OR:1.004, 95% CI:1.001-1.008, P:0.024).

30-day follow-up

On 30-day follow-up interviews, none of the patients reported any serious complications related to the received contrast agents. Also, in all the patients with abnormally increased serum creatinine during the first postprocedural days, the creatinine level had returned to baseline levels.

Discussion

Our study demonstrated that the incidence of CIN following coronary angiography was similar to the three different types of contrast media: Iodixanol, Iopromide, and Iohexol. In addition, by evaluating several probable risk factors in the history of the patients, we found pre-existing renal insufficiency, smoking, and the volume of contrast media as independent predictors of CIN.

CIN is one of the major complications of coronary angiography which may lead to increased morbidity and mortality in these patients. Though the exact mechanism is still unknown, several pathophysiologic processes have been proposed including the direct nephrotoxicity of the contrast media on the tubular epithelium and glomerular endothelium, increased viscosity, hypoxic injury, and oxidative stress [11]. The type of contrast media used is one of the factors that can affect the incidence and severity of CIN. Since high osmolality contrast agents are now almost out of routine practice due to their higher adverse effects, the iso and low- osmolality agents are exclusively used in diagnostic and interventional techniques. In our study, the overall rate of CIN was 4% with a subsequent decrease in the baseline creatinine in the 30 days in all the affected patients. This implies the general safety of these low and iso-osmolar agents regarding kidney function and is consistent with the previous estimates of its incidence in the literature [11,12].

We observed that there was no significant difference in the incidence of CIN in groups of patients receiving Iopromide, Iohexol, or Iodixanol. This is in line with the notion of most previous studies, that demonstrated a comparable rate of CIN with iso and low-osmolar agents in patients with normal renal function or samples including patients with both normal and abnormal renal function [13-15]. Although the iso-osmolar iodixanol was traditionally thought to have a lower rate of CIN, its higher viscosity might have led to a similar risk of CIN, despite the superior osmolality characteristics [11]. On the other hand, according to the literature, the rate of CIN has been different with different low osmolar agents. In a study by Karlsberg., *et al.* on patients undergoing digital angiography for suspected peripheral arterial occlusive diseases, the CIN occurred more frequently with the low-osmolar agents than with Iodixanol. However, further analysis of their data revealed that this significant difference was caused primarily by iopamidol, and the rest of the low-osmolar agents including iopromide, iohexol, and ioversol had a similar risk of CIN as iodixanol [16]. Also in a meta-analysis by Reed., *et al*. pooling 16 trials, Iodixanol did not show any reduction in CIN compared to the group of low osmolar agents, while compared to iohexol and ioxaglate, it showed a significant reduction in the risk of CIN [17].

Despite studies on patients with intact renal function, several studies on patients with pre-existing renal insufficiency, have reported that low-osmolar agents are associated with a higher risk of CIN compared with iodixanol [18-20] and have suggested that the use of the more expensive iodixanol can be kept for the high-risk patients.

According to our results, pre-existing renal disease, smoking, and the volume of contrast were independent predictors of CIN. Similar to our findings, several studies have shown underlying renal insufficiency to be among the strongest risk factors for CIN [11,21], making a preprocedural evaluation of the renal function a crucial step in the contrast requiring interventions. Sensibly, the dose of contrast media has also been reported by many studies and risk predictive models as a major risk factor for CIN [11,14,22].

Other common strong risk factors introduced by the literature include advanced age, heart failure, hypo and hypertension, diabetic nephropathy, anemia, and concomitant use of nephrotoxic medications [11,22,23]. Uniquely, our results revealed smoking as an independent predictor of CIN. This can be explained by known adverse effects of smoking including endothelial damage and increased oxidative stress, both of which are suggested as mechanisms for CIN [11].

Conclusion

The three commonly used contrast media, iodixanol, iohexol, and iopromide had low rate of nephrotoxicity in patients undergoing coronary angiography with or without PCI; and there was no significant difference between these agents regarding the rate of CIN.

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