Contrast-induced nephropathy in patients undergoing percutaneous coronary intervention, iso-osmolar non-ionic contrast agent versus low-osmolar ionic contrast agent

Nefropatia induzida por contraste não iônico isosmolar *versus* iônico de baixa osmolaridade em pacientes após intervenção coronária percutânea

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ABSTRACT – Background: Coronary angiography is an advance in the management of a variety of heart conditions, but iodinated contrast injection can lead to contrast-induced nephropathy, especially in high-risk populations. There is still no consensus on the best type of contrast agent to be used. The objective of this study was to evaluate the occurrence of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention, comparing a low-osmolar contrast agent with an iso-osmolar contrast agent. **Methods:** This was a single center, longitudinal, prospective and non-concurrent study. The type of contrast agent used in the procedure and the clinical variables of the patients were associated with the occurrence of contrast-induced nephropathy using the Chi-square test. A logistic regression model was developed for multivariate analysis. **Results:** A total of 374 percutaneous coronary interventions were performed with only one type of contrast agent, 275 using a low-osmolar contrast agent, and 99 using an iso-osmolar contrast agent. The mean age was 61.86 years; 66.3% of patients were male, 38.5% were diabetic, 24.3% had chronic kidney disease, and 44.7% had acute coronary syndrome. The iso-osmolar contrast agent was associated with a higher occurrence of nephropathy when compared to the low-osmolar contrast agent (12.1% versus 5.8%; $p=0.041$; $p=0.047$ in multivariate analysis), with a 2.3 times greater chance of complication. Age ($p=0.045$) and diabetes ($p=0.088$) were also relevant for the occurrence of nephropathy. One patient in each group progressed to hemodialysis during the in-hospital period. **Conclusion:** The iso-osmolar non-ionic contrast agent is associated with a higher occurrence of contrast-induced nephropathy when compared to the low-osmolar ionic contrast agent.

Keywords: Kidney diseases; Percutaneous coronary intervention; Contrast media

RESUMO – Introdução: A angiografia coronária é um avanço no manejo de uma série de condições cardíacas, porém a injeção de contraste iodado pode levar à nefropatia induzida por contraste, principalmente em populações de alto risco. Ainda não há consenso sobre qual o melhor tipo de contraste a ser utilizado. O objetivo deste estudo foi avaliar a ocorrência de nefropatia induzida por contraste em pacientes submetidos à intervenção coronária percutânea, comparando contraste de baixa osmolaridade com contraste isosmolar. **Métodos:** Estudo unicêntrico, longitudinal, prospectivo e não concorrente. O tipo de contraste utilizado no procedimento e as variáveis clínicas dos pacientes foram associados à ocorrência de nefropatia induzida por contraste, utilizando teste qui-quadrado; um modelo de regressão logística foi desenvolvido para a análise multivariada. **Resultados:** Um total de 374 intervenções coronárias percutâneas utilizou apenas um dos tipos de contraste, sendo 275 o de baixa osmolaridade e 99 o isosmolar. A média de idade foi 61,86 anos; 66,3% dos pacientes eram do sexo masculino, 38,5% eram diabéticos, 24,3% tinham doença renal crônica e a apresentação clínica foi de síndrome coronariana aguda em 44,7%. O contraste isosmolar foi associado a maior ocorrência de nefropatia quando comparado ao de baixa osmolaridade (12,1% *versus* 5,8%; $p=0,041$; $p=0,047$ na análise multivariada), com chance 2,3 vezes maior da complicação. Idade ($p=0,045$) e diabetes

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($p=0,088$) também foram relevantes para ocorrência de nefropatia. Um paciente em cada grupo evoluiu para hemodiálise no período intra-hospitalar. **Conclusão:** O contraste não iônico isomolar é associado a maior ocorrência de nefropatia induzida por contraste, quando comparado ao contraste iônico de baixa osmolaridade.

Descritores: Nefropatia; Intervenção coronária percutânea; Meios de contraste

INTRODUCTION

Coronary angiography for diagnostic or therapeutic purposes is an advance in the management and risk stratification of a variety of heart conditions.¹⁻⁴ Despite the benefits, this method requires iodinated contrast injection, which in some patients may lead to contrast-induced nephropathy (CIN), one of its main complications.^{3,5-12}

The overall incidence of CIN has been declining in recent decades, but still reaches 12% to 28% in high-risk populations such as elderly patients with diabetes mellitus (DM) and chronic kidney disease (CKD), and even 50% in very high risk patients with multiple comorbidities.^{1,2,3,5-10}

The osmolality of the contrast medium apparently plays a role in the occurrence of this complication, with a benefit of use of low-osmolar non-ionic and iso-osmolar non-ionic contrast agents. However, there is no consensus on which contrast agent is associated with lower occurrence of CIN.^{1,6-8,13}

Studies like RECOVER⁶ (Renal Toxicity Evaluation and Comparison Between Visipaque and Hexabrix in Patients With Renal Insufficiency Undergoing Coronary Angiography) and NEPHRIC⁸ (Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media) demonstrated a benefit of use of iso-osmolar contrast agents in high risk populations, but these are small studies with 300 and 129 patients, respectively, and there are still uncertainties regarding the existence and significance of this benefit.^{1,2,11,14-20}

The results of clinical studies and the lack of consensus regarding the superiority of one type of contrast agent over another, especially in the Brazilian population, require further research on the subject.

The objective of this study was to evaluate the occurrence of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention comparing a low-osmolar contrast agent with an iso-osmolar contrast agent.

METHODS

This study was evaluated and approved by the Research Ethics Committee of the *Instituto Dante Pazzanese de Cardiologia* (protocol 4689/2016; CAAE 58593116.2.0000.5462).

Population

We conducted a longitudinal, prospective, non-concurrent evaluation of the percutaneous coronary intervention

(PCI) data from January to December 2016 in our organization, where only one type of contrast agent was used in each procedure, namely ioxaglate (Hexabrix®, Guerbet), a low-osmolar ionic contrast agent, or iodixanol (Visipaque™, GE Healthcare), an iso-osmolar non-ionic contrast agent. Since there were no specific protocols in the organization for choosing either contrast agent, the contrast agent was chosen at the operator's discretion, and the cases were included consecutively and not randomly.

We included patients older than 18 years with PCI for stable coronary artery disease (CAD), stable angina or silent ischemia, or acute coronary syndrome (ACS), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina (UA), and ST-segment elevation myocardial infarction (STEMI). We excluded patients who used more than one type of contrast agent during the procedure or used a high-osmolar contrast medium; patients who were already on hemodialysis; and patients who had no data regarding creatinine values before or after the procedure.

Outcomes

The primary endpoint was to compare the incidence rate of CIN, defined as creatinine elevation above 25% or a 0.5 mg/dL increase from baseline, in patients undergoing PCI,¹⁴ comparing the use of an iso-osmolar non-ionic contrast agent with the use of a low-osmolar ionic contrast agent.

As secondary endpoints, we evaluated the association of CIN with the clinical variables of the population, age, hypertension (HTN), DM, dyslipidemia, CKD, clinical presentation, stable ACS or CAD, smoking, and control creatinine collection time after PCI. We also evaluated the need for hemodialysis in the short-term follow-up of 30 days.

Renal function assessment

To determine pre-procedural creatinine levels, blood samples were collected in the week of the procedure as a routine test for patients undergoing PCI. As for post-procedural creatinine levels, blood samples were collected on the days following the procedure, in most cases while the patient was still hospitalized. To determine the occurrence of CIN, we preferably used the creatinine levels measured from 48 hours up to 72 hours after the procedure. The creatinine collection time after PCI was counted in hours from procedure completion to laboratory collection time. All tests were collected and analyzed by the organization laboratory, regardless of the time of collection. Creatinine clearance (CrCl) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.²¹ CKD was defined as CrCl <60mL/minute before the procedure.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and a Wilcoxon-Man-Whitney test was used when a comparison of subgroups was required. Categorical

variables were described as frequencies and/or percentages and compared with the Chi-square test. Multiple linear regression model was performed to assess the association of variables with the primary endpoint. The variables associated with the endpoint and those closely related ($p < 0.1$) were included in the model. No specific subgroups other than the variables described were determined. A p value < 0.05 was considered statistically significant. The analysis was performed using the IBM Statistical Package for Social Science (SPSS) software, version 22.

RESULTS

From January to December 2016, we evaluated 382 PCI procedures. Of these, 280 (73.3%) were performed using a low-osmolar ionic contrast agent (ioxaglate), and 102 (26.7%) were performed using an iso-osmolar non-ionic contrast agent (iodixanol). Eight procedures were excluded from the analysis, 5 for not having pre-procedural creatinine data and 3 for being on hemodialysis regimen, resulting in a total of 374 procedures included in the final analysis.

The mean age of patients was 61.8 ± 10 years, ranging from 29 to 93 years; 66% were male, 86% had HTN, and 38.5% were diabetic. ACS was present in 44.7%, and 44.1% of patients had previous acute myocardial infarction (MI). Table 1 shows the clinical characteristics of the total population, and the clinical characteristics according to the type of contrast agent used. Patients who used a low-osmolar

contrast agent had a higher incidence of hypertension, whereas those who used an iso-osmolar contrast agent had a higher incidence of prior PCI and peripheral obstructive arterial disease.

The mean pre-procedural creatinine value was 0.98 ± 0.47 (0.95 ± 0.44 for low-osmolar versus 1.05 ± 0.54 for iso-osmolar; $p = 0.731$) and the mean post-procedural creatinine value was 1.03 ± 0.55 (0.99 ± 0.46 for low-osmolar versus 1.12 ± 0.71 for iso-osmolar; $p = 0.316$). There was a significant increase in serum creatinine levels before and after the procedure, both in the total population and when comparing the use of the two types of contrast agent ($p < 0.001$ for the three interactions). The CrCl was higher in patients who used the low-osmolar ionic contrast agent (85.8 ± 31.9 mL/minute versus 72.5 ± 38.2 mL/minute; $p < 0.001$). It is noteworthy that, on average, patients were at the same stage of CKD and there was no difference between the groups among those with CrCl < 60 mL/minute ($p = 0.059$).

Although relatively low when compared to the expected amounts during PCI procedures, the mean contrast agent volume used was higher in the low-osmolar ionic contrast agent group (93.4 ± 56 mL versus 86.4 ± 46 mL; $p < 0.001$). Most patients had the procedure performed radially (52.7% in the low-osmolar group versus 58.6% in the iso-osmolar group), and 54% of patients in each group had multivessel disease. Data regarding PCI are found in table 2.

The primary endpoint, CIN, occurred in 28 (7.5%) patients. Of these, 16 (4.3%) used low-osmolar ionic contrast agent, and 12 (3.2%) used iso-osmolar non-ionic contrast

Table 1. Basal characteristics of the population

Characteristics	Total (n=374)	Low-osmolar (n=275)	Iso-osmolar (n=99)	p-value
Age	61.86 ± 10.47	61.49 ± 10.54	62.88 ± 10.23	0.344
Male	248 (66.3)	180 (65.5)	68 (68.7)	0.615
HTN	324 (86.6)	244 (88.7)	80 (80.8)	0.047
Diabetes mellitus	144 (38.5)	105 (38.2)	39 (39.4)	0.832
Dyslipidemia	252 (67.4)	187 (68.0)	65 (65.7)	0.670
CKD	91 (24.3)	60 (21.8)	31 (31.3)	0.059
Smoking habit	83 (22.2)	64 (23.3)	19 (19.2)	0.402
Prior acute MI	156 (44.1)	123 (44.7)	42 (42.4)	0.692
Prior PCI	59 (15.8)	37 (13.5)	22 (22.2)	0.040
Prior CABG	41 (11.0)	31 (11.3)	10 (10.1)	0.749
PAD	10 (2.7)	4 (1.5)	6 (6.1)	0.015
Clinical presentation				0.066*
NSTEMI/UA	115 (30.8)	78 (28.4)	37 (37.4)	
STEMI	52 (13.9)	37 (13.4)	15 (15.1)	
Stable angina	171 (45.7)	134 (48.7)	37 (37.4)	
Silent ischemia	36 (9.6)	26 (9.5)	10 (10.1)	

Results expressed as mean $\pm$ standard deviation or n (%).

* p-value for acute coronary syndrome versus stable coronary artery disease.

HTN: hypertension; CKD: chronic kidney disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PAD: peripheral obstructive arterial disease; ACS: acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina; STEMI: ST-segment elevation myocardial infarction.

Table 2. Characteristics of percutaneous coronary intervention

Characteristic	Low-osmolar (n=275)	Iso-osmolar (n=99)
Radial access approach, n (%)	145 (52.7)	58 (58.6)
Disease severity, n (%) [*]		
Single vessel	127 (46.2)	46 (46.5)
Two-vessel	100 (36.4)	37 (37.4)
Three-vessel	48 (17.4)	17 (17.1)
Target vessel, n (%)		
LMCA	8 (2.9)	1 (1.1)
Left anterior descending	142 (51.6)	54 (54.5)
Circumflex	82 (29.8)	35 (34.4)
Right coronary	92 (33.4)	30 (30.3)
Bypass graft	5 (1.8)	2 (2.1)
Number of treated vessels, n (%)		
1	224 (81.5)	78 (78.7)
2	48 (17.4)	19 (19.2)
3	3 (1.1)	2 (2.1)
Type of lesion, n (%)		
Chronic occlusion	18 (6.6)	5 (5.1)
In-stent restenosis	9 (3.3)	2 (2.1)
Bifurcation	75 (27.3)	27 (27.2)
Stents		
Number per patient	1.42	1.43
Mean diameter, mm	2.9	2.9
Mean length, mm	23.6	23.8
Drug-eluting stents, n (%)	270 (98.1)	98 (98.9)

^{*} Epicardial vessel or one of its branches with at least 50% stenosis.
LMCA: Left main coronary artery.

agent. The use of iso-osmolar contrast agent was associated with the occurrence of CIN (12.1% versus 5.8%; $p=0.041$) when compared to the use of low-osmolar contrast agent. Only one patient in each contrast agent group required hemodialysis during hospitalization. The only clinical characteristic associated with CIN was age. Patients aged ≥ 70 years had a higher occurrence of the event (12.4% versus 6.0%; $p=0.045$). Of the other clinical variables, only patients with DM had some tendency to be associated with the occurrence of CIN and were included in the multivariate analysis (10.4% versus 5.7%; $p=0.088$).

The mean time for creatinine collection after the procedure was 29.07 ± 16.42 hours, ranging from 12 to 72 hours. This time was significantly longer in those patients who developed CIN (16.8% versus 3.1%; $p<0.001$).

Multivariate logistic regression analysis considered all variables with at least one p -value below 0.1 in reference to the occurrence of CIN. The use of iso-osmolar non-ionic contrast agent and longer creatinine collection time after the procedure remained associated with the occurrence of CIN after multivariate correction. Table 3 presents the results of this analysis.

Table 3. Multivariate linear regression analysis

	OR	95%CI	p-value
Type of contrast agent – iso-osmolar	2.295	1.012-5.205	0.047
Age	1.028	0.990-1.068	0.151
Creatinine collection time	1.039	1.017-1.061	<0.001
Diabetes mellitus	1.869	0.831-4.204	0.130

DISCUSSION

The major findings of our study were that in patients undergoing PCI, the use of an iso-osmolar non-ionic contrast agent, iodixanol, was associated with a higher incidence of CIN, when compared to the use of a low-osmolar ionic contrast agent, ioxaglate (12.1% versus 5.8%; $p=0.041$; $p=0.047$ in the multivariate analysis), with a 2.3-fold increase in the chance of CIN in patients who used the former contrast agent. The total incidence of CIN in our population was low considering its high risk, with a total of 28 patients (7.5%) presenting the outcome. Patients who developed CIN in our population were older than those without the endpoint.

Our data do not coincide with the RECOVER⁶ study results, which showed reduction in the incidence of CIN with the use of iso-osmolar contrast agent, when compared with the use of low-osmolar contrast agent (7.9% versus 17.0%; $p=0.021$). In that study, the use of ioxaglate was associated with a 2.65-fold increase in CIN – virtually the opposite of our findings, which showed a 2.3-fold increase in CIN incidence in those using an iso-osmolar contrast agent. Aspelin et al. also found such results in the NEPHRIC,⁸ a prospective, multicenter, double-blind study, which demonstrated a reduction in the occurrence of CIN (3% versus 26%; $p=0.002$) in patients using iodixanol, when compared to the use of iohexol, a low-osmolar contrast agent. Both studies showed significant reduction in high-risk subgroups, as in CKD and diabetics patients.^{6,8}

Despite these data, Morcos conducted a meta-analysis of prospective, randomized, double-blind studies, and concluded that all types of contrast agents are nephrotoxic and, due to the methodological heterogeneity of different studies, it is difficult to determine if one contrast agent is truly superior to the other.¹⁵ Biondi-Zoccai et al. recently evaluated 42 studies, with a total of 10,048 patients and 7 types of contrast agents. In this analysis, iodixanol showed low risk of CIN, similarly to the low-osmolar contrast agents.¹⁴

We found a low total incidence of CIN in our study (7.5%), which differs from the literature, in which the mean incidence rates found ranges from 12.3% to 15.9%^{6,8-10} in high risk populations. Using meta-analysis, McCullough et al. demonstrated that the incidence rate of CIN in a sample of 2,727 patients was 4.9%, with an increase to 11.2% in patients with CKD, and to 19% in patients with CKD and DM.¹³ Mehran et al. evaluated patients who were divided

into risk scores and demonstrated that the incidence of CIN can exceed 50% in patients at very high risk.⁹ There are some possible explanations for this finding. In our institution, we use hydration protocols for patients with CKD and those undergoing PCI, and we also reduce the contrast agent volume used during the procedure, which, on average, was less than 100mL for both groups. Another explanation for this is that, in our study, the mean post-procedure blood sample collection time to evaluate creatinine levels was 29 hours. The peak incidence of CIN is between 48 and 72 hours after the use of iodinated contrast agents,^{1,2,5,11} and this may hinder the detection of some cases. In our study, the patients who developed CIN had longer collection time than those who had no renal function impairment ($p < 0.001$). This may have caused some reduction in the occurrence of CIN, but does not appear to have specifically influenced any of the contrast agent groups, as there was no difference between them.

Age is considered a risk factor for the development of CIN. Studies often consider patients over 75 years to be at increased risk,^{5,9,10} but the risk increases continually with age, and even patients from 60 to 75 years old are already at high risk.^{22,23} In our study, older patients developed CIN, and an association with the occurrence of this event was found in patients from 70 years old onwards, though, in the multivariate analysis, this association was not significant.

Our finding is clinically relevant because the occurrence of CIN is associated with prolonged hospital length-of-stay, delayed treatment and procedures, increased bleeding, MI, and death in the short and long-term follow-up.^{3,5,6,11} Although the literature presents studies which contradict our findings,^{6,8} they are small studies (<300 patients) and their main meta-analysis does not show clear benefit of one type of contrast agent over others.¹⁴ We still lack data from a large randomized, long-term follow-up study to confirm benefits, such as reduced CIN incidence and possible clinical benefits in this population, with each type of contrast agent.

Our study has some limitations. First, it is a single center study, with local specific protocols for PCI and CIN prophylaxis. All patients with CrCl <60mL/minute were hydrated with 0.9% saline at an infusion rate of 0.5 to 1mL/kg/hour, 12 to 24 hours before and after the procedure. Second, an early blood sample collection for measuring creatinine levels after the procedure, averaging 29 hours, may have influenced the occurrence of low CIN for a high-risk population. This is due to the blood collection and hospital discharge routine of the organization on the day following the intervention in elective patients, with only a few patients having elective blood collections or more prolonged hospital length-of-stay. Although there was a difference in collection time between patients with CIN and those without CIN, there was no significant difference between both contrast agent groups, attenuating its influence on the results. Finally, we cannot exclude the possibility that these findings are due to chance and possibly related to an imbalance in the characteristics of the population, to the total number of patients and to the low occurrence of events. To this end, a study of

more than 2,000 patients is being conducted at our institution to assess which type of contrast agent has the best renal and clinical protection profile.

CONCLUSION

The use of an iso-osmolar non-ionic contrast agent, iodoxanol, in the scenario of PCI was associated with a higher incidence of contrast-induced nephropathy, when compared to the use of a low-osmolar ionic contrast agent, ioxaglate.

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None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

AUTHORS' CONTRIBUTION

Conception and design of the study: RMJ, AA, FF, LFT and JRCJ; data collection: RMJ and RP; data interpretation: RMJ and RLS; writing of the text: RMJ, SNB, AGMRS and RLS; approval of the final version to be published: RMJ and JRCJ.

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