Contrast-induced nephropathy after computed tomography

Nefropatia induzida por contraste após tomografia computadorizada

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Abstract

Introduction: Contrast induced nephropathy is the third most prevalent preventable cause of acute kidney injury in hospitalized patients. It defined as an absolute increase in serum creatinine ≥ 0.5 mg/dL and relative ≥ 25% increase. **Objective:** We studied the risk factors to intravenous injection contrast nephropathy after computed tomography. **Methods:** We studied 400 patients prospectively. **Results:** The incidence of contrast induced nephropathy, with an absolute or a relative increase were 4.0% and 13.9%, respectively. Diabetes and cardiac failure were independent risk factors for CIN a relative increase de serum creatinine (O.R.: 3.5 [95% CI: 1.92-6.36], $p < 0.01$, 2.61 [95% CI: 1.14-6.03%], $p < 0.05$, respectively). **Conclusions:** We showed association between uses of intravenous injection contrast after computed tomography with acute injury renal, notably with diabetes and heart failure.

Keywords: contrast media; risk factors; tomography.

Resumo

Introdução: Nefropatia induzida por contraste é a terceira causa de lesão renal aguda em pacientes hospitalizados. Ela é definida como: um aumento absoluto da creatinina sérica ≥ 0,5 mg/dL e relativo em ≥ 25%. **Objetivo:** Nós estudamos os fatores de risco associados à nefropatia do contraste após tomografia computadorizada. **Métodos:** Analisamos prospectivamente 400 pacientes submetidos ao contraste endovenoso na tomografia computadorizada. **Resultados:** A incidência de nefropatia por contraste variou de 4 a 13,9%, conforme o critério de aumento da creatinina sérica. Diabetes e insuficiência cardíaca foram associados significativamente no aumento absoluto da creatinina sérica (O.R.: 3,5 [95% CI: 1,92-6,36], $p < 0,01$, 2,61 [95% CI: 1,14-6,03%], $p < 0,05$, respectivamente). **Conclusão:** Encontramos uma relação direta da infusão de contraste endovenoso na tomografia computadorizada e injúria renal, notadamente com diabetes e insuficiência cardíaca.

Palavras-chave: fatores de risco; nefropatia induzida por contraste; tomografia.

Introduction

Contrast-induced nephropathy (CIN) is an important cause of acute kidney injury (AKI) in hospitalized patients. There are several risk factors associated with CIN after arterial infusion: high doses of iodine; diabetes mellitus (DM); old-age, chronic renal failure (CKD); female gender, heart failure (HF), association with nephrotoxic drugs, etc.[1-6]

CIN pathogenesis is related to direct toxic effect of contrast medium on the tubular epithelial cells and results from direct hemodynamic disturbances in renal blood flow. Renal tubules are less prone to injury when isosmotic contrast medium is used as compared to low-osmolality contrast media. Intravascular contrast administration effects on renal blood flow were biphasic. The initial vasodilatation turns into the longest lasting phase of reduced renal blood flow, consequent to vasoconstriction and hypoxia. Moreover, there is a release of endogenous factors such as endothelin, adenosine, free radicals, Ca^{2+} ions, and the glomerular filtration rate issue.[6,7]

However, the CIN incidence in computed tomography (CT) is quite complex. The use of intravenous contrast to enhance

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imaging has increased substantially in recent years. Studies have described a CIN incidence between 5 and 13% in outpatients after venous contrast injection to enhance CT scan images. These studies are limited by their retrospective design and patient selection bias.[3,5,8,9]

This study evaluated CIN incidence in hospitalized patients after CT scan with intravenous contrast injection, its relation with classic risk factors (DM, HF, old age, etc.) and contrast volume with variations in serum creatinine (SCr) levels.

Methods

Study Population

Our cohort study allocated 400 hospitalized patients from a single center (Hospital São Lucas PUCRS) between January 01, 2007 and March 31, 2008. All patients underwent CT scan with hyperosmolar intravenous contrast (59.285 g, meglumine 15.1 g/100 mL, iodine content of 300 mg/mL, osmolality of 1650 mOsm/kg H_2O, *Telebrix 30 Laboratory Guebert*).

Inclusion criteria for this study were: age over 18 years and hospitalization.

Exclusions criteria were: drugs that can interfere with the SCr assay (e.g.: cephalosporins, barbiturates, chemotherapeutic agents) and its secretion (e.g.: trimethoprim, cimetidine).

All patients signed consent forms. The local ethics committee approved this study.

Study Execution

SCr values were obtained from a kinetic colorimetric compensated Jaffe technique (Roche Modular, Meylan; compensation according to manufacturer's recommendations). We evaluated the assay method's inaccuracy (intra-assay coefficient was 0.7%; inter-assay coefficients were 4.0% at low SCr (0.51 - 0.71 mg/dL) and 1.5% at high SCr concentrations (6.5 mg/dL), respectively. SCr was tested before and 48 hours after intravenous contrast injection.

To estimate GFR (eGFR), we used the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula:[6]

$141 \times \min(SCr/k, 1)^{\alpha} \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age}$ [x1.018 if female] [x1.159 if black], where SCr is serum creatinine (in mg/dL), k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/k or 1, and max is the maximum of SCr/k or 1.

We did not divide our sample into CKD groups according to the KIDGO criteria because of the small number of patients with eGFR < 60 mL/min/1.73 m².

Potential risk factors for CIN were considered based on the concepts and terminology from the American College of Radiology (ACR):[5] DM, neoplasia, HF, CKD, female gender, low mean arterial blood pressure upon examination (MBP < 80 mmHg), CKD (eGFR < 60 mL/min/1.73 m²), old-age (≥ 65 years), obesity (BMI ≥ 30 kg/m²), anemia (Hematocrit < 36%). We defined CIN prophylaxis as the use of parenteral hydration with saline solution at a dose of 1 mL/kg/h 6 hours prior to the procedure, and continued up to 12 hours after it.

Outcomes

The primary outcomes was CIN incidence and association with risk factors. Secondary outcome was SCr variation vis-à-vis contrast volume per 1.73 m² of BSA.

Statistical analysis

Our data was submitted to double entry, checking for inconsistencies.

We used backward stepwise linear and multivariable logistic regression, comparing the new variable to those previously reported. A p value < 0.05 was considered statistically significant. The analyses were performed using R for Windows, version 3.1.1 (*R-Cran project*) with the MASS package for Windows.

Results

Baseline Clinical Characteristics

The baseline clinical characteristics of those 400 patients are show on the Table 1. Upon inclusion in the cohort, the participants' mean ages were 59.2 ± 14.8 years. Elderly patients and male gender accounted for 40.2% and 50.4% respectively, with Caucasian predominance at 80.5%. Mean BMI was 24.36 ± 1.74 kg/m², with underweight and obesity prevalences of 14.8% and 13.6%, respectively.

Most intravenous contrast-enhanced CT examinations were associated with malignancies (n = 249, 62.25%) in the chest, and chest-abdomen (n = 289, 72.25%). See details on Table 2. Mean contrast volume was of 142.2 ± 37.7 mL/1.73 m² of BSA.

Of the entire sample, 25 patients (6.25%) took metformin on the contrast injection day. Only 97 (24.25%) patients received intravenous hydration (Table 1).

Table 1 Demographic data set

Characteristics	Patients (N = 400)
Age (years)	59.2 ± 14.8
Old-aged	161 (40.25%)
Female gender	198 (49.50%)
Ethnicity	
White	323 (80.75%)
Afro-Brazilian	77 (19.25%)
Body Mass Surface (m^2)	1.74 ± 0.21
Body Mass Index (kg/m^2)	24.36 ± 1.74
Obesity	59 (14.75%)
SCr (mg/dL)	0.96 ± 0.38
eGFR < 60 mL/min/1.73 m^2	78 (19.50%)
Diabetes	73 (18.25%)
Heart Failure	30 (7.50%)
Neoplasia	249 (62.25%)
MBP < 80 mmHg	60 (15%)
Hematocrit < 36%	200 (50%)
Contrast Volume mL/1.73 m^2	142.2 ± 37.7
Metformin	25 (6.25%)
Prophylaxis	97 (24.25%)

eGFR: Estimated glomerular filtration rate; SCr: Serum creatinine; MBP: Mean arterial blood pressure.

Table 2 Type of computerized tomography and volume contrast

Localization	N	Median volume contrast per 1.73 m^2 [IQR]*
Cranial	31(7.75%)	64.0 [54.5; 120.0]
Abdomen	64 (16%)	152.0 [105.5; 198.5]
Thorax	162 (40.5%)	156.0 [49.5; 229.5]
Thoracoabdominal	127 (31.75%)	198.5 [134.5; 249.0]
Others	16 (4%)	132.0 [30.0; 254.0]

We found an increase in baseline SCr of 25% in 61 (15.25%) patients and an absolute increase of 0.5 mg/dL in only 15 (3.75%) patients in our sample (Table 3).

Procedures and variation in renal function

Multivariable logistic regression

After using intravenous contrast for CT, we found an association between absolute increase in SCr ≥ 0.5 mg/dL (Table 4) and ≥ 25% (Table 5) and the following factors: old age, DM, female gender, obesity, HF, CKD, neoplasia and anemia.

Multivariate analysis revealed a relationship between an absolute increase in SCr ≥ 0.5 mg/dL and

Table 3 Incidence of contrast nephropathy and markers of renal injury

Outcome	
Creatinine (mg/dL)	
Baseline	0.9 ± 0.38
48 hours	1.0 ± 0.47
eGFR (mL/min/1.73 m^2)	
Baseline	93.43 ± 14.8
48 hours	91.95 ± 14.7
Occurrence of CIN	
SCr increases ≥ 25%	61 (15.75%)
SCr increases ≥ 0.5 mg/dL	15 (3.75%)

eGFR: Estimated glomerular filtration rate; SCr: Serum creatinine; MBP: Mean arterial blood pressure.

Table 4 Risk factors to contrast nephropathy (SCr increases ≥ 0.5 mg/dL)

Risk factors	OR	95% CI	*p*
Old-age	6.3	1.8 to 22.5	< 0.01
Diabetes	10.2	3.4 to 31.0	< 0.01
Female gender	0.9	0.3 to 2.5	0.8
Obesity	1.4	0.4 to 5.5	0.5
Heart failure	13.8	4.5 to 42.0	< 0.01
eGFR < 60 mL/ min/1.73 m^2	3.9	1.3 to 11.0	< 0.05
Neoplasia	0.4	0.1 to 1.1	0.6
MBP < 80 mmHg	0.4	0.0 to 2.0	0.4
Hematocrit < 36%	0.6	0.2 to 1.9	0.4

SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; MBP: Mean arterial blood pressure; CI: Confidence interval; OR: Odds ratio.

DM (O.R.: 10.22 [95% CI: 3.37-30.92], $p < 0.01$); old-age (OR 6.27 [95% CI: 1.74-22.57], $p < 0.05$) and HF (3.9 [95% CI: 1.36-11.00], $p < 0.01$) (Table 4).

The relative variation (Table 5) of SCr was associated with diabetes (O.R.: 3.5 [95% CI: 1.92-6.36], $p < 0.01$) and HF (OR 2.61 [95% CI: 1.14-6.03%], $p < 0.05$). However, it was not significant vis-à-vis old age and CKD (Table 5).

Regardless of reports in the medical literature, we did not find associations between female gender, obesity, neoplasia, MBP < 80 mmHg, anemia and CIN (Tables 4 and 5).

Multivariate analysis regression model and the impact on renal function fluctuation

Table 6 depicts the impact of contrast volume in relation to SCr increase. In the entire sample there was no difference in SCr after 116 mL of venous contrast injection per 1.73 m^2 of BSA (model Ÿ1). However,

Table 5 Risk factors to contrast nephropathy (SCr increases ≥ 25%)

Risk factors	OR	95% CI	*p*
Old-age	1.0	0.6 to 1.8	0.9
Diabetes	3.5	1.9 to 6.4	< 0.01
Female gender	1.5	0.8 to 2.6	0.1
Obesity	1.7	0.8 to 3.3	0.1
Heart failure	2.6	1.1 to 5.9	< 0.05
eGFR < 60 mL/min/1.73 m^2	0.5	0.2 to 1.0	0.1
Neoplasia	0.8	0.4 to 1.3	0.3
MBP < 80 mmHg	0.3	0.0 to 1.2	0.2
Hematocrit < 36%	0.8	0.5 to 1.4	0.5

SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; MBP: Mean arterial blood pressure; CI: Confidence interval; OR: Odds ratio.

Table 6 Impact on SCr variation (percentage per 100 mL/1.73 m^2 of contrast)

Risk factors	Model	*p*
Entire population	Ÿ1 = 116X + 0.07	0.3
Diabetes	Ÿ2 = 112X + 0.22	< 0.01
Heart Failure	Ÿ3 = 114X + 0.23	< 0.01
eGFR < 60 mL/min/1.73 m^2	Ÿ4 = 118X + 0.01	0.8
Old-age	Ÿ5 = 116X + 0.09	0.2

SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate.

DM and HF had a significant increase of 22% and 23% ($p < 0.01$) per 112 and 114 mL of intravenously injected contrast agent per 1.73 m^2 of BSA, respectively (model Ÿ2 and Ÿ3). Patients with eGFR < 60 mL/min/1.73 m^2 and the elderly in the sample did not show significant variation vis-à-vis contrast agent dose (model Ÿ4 and Ÿ5).

Discussion

CIN-related papers have been published since the 50's, notably after arterial contrast injection started. However, only a handful of studies have investigated CIN with intravenous contrast injection for CT.[1-5,10] These studies described similar risk factors for patients undergoing CT and angiographic exams. Nyman *et al.*[10] reported a CIN incidence of 6.4% after CT and higher CIN incidences in patients with impaired GFR.

Our results show CIN incidence after CT of 3.75 and 15.75%, with CIN defined as the absolute or relative increase of SCr, respectively. Thomsen *et al.*[11] described that these two definitions of CIN are not interchangeable, because SCr is not an adequate marker for CIN. Thus, > 50% of renal function must be lost before an elevation in SCr is detected. In addition, SCr does not accurately depict GFR until a steady state has been reached, which may require several days[12] - this could explain the different CIN incidence found in our study. The Acute Kidney Injury Network (AKIN) suggested two separate CIN endpoints using both absolute and relative SCr alterations.[6] Their proposed diagnostic criteria for AKI include an absolute increase in the SCr level of ≥ 0.3 mg/dL. However, calculations by Waikar & Bonventre[13] showed that increases in SCr of 0.3 mg/dL are only significant when they occur within 24 h; and 0.5 mg/dL at 48 h after CT may be a more appropriate cut-off point. Moreover, the medical literature is based on the concepts and terminology from the American College of Radiology (ACR) in reference to CIN studies, this report will do the same.[5] However, we recognize that the clinical effects of slightly different definitions of CIN and AKI have yet to be clarified.[6]

Our results confirmed significantly classical risk factors to CIN after CT as being: CKD, DM and HF. Mehran *et al.*[14] showed an incidence of 8.8% and 5.2%, after arterial injection in patients with CKD and DM, respectively. In patients with CKD, HF and the elderly, SCr rises more steeply when hemodynamic changes occur or contrast is administered.[4,7]

Our study demonstrated a statistically significant association, although low, between contrast medium volume and CIN, notably in DM and HF. It is opposite to the findings reported by other publications.[8,10,15-17] Nyman *et al.*[10] suggested a dose in grams of iodine numerically equal to the eGFR value in mL/min during percutaneous coronary intervention. These authors described a CIN frequency of 12% at an iodine dose (in grams)/GFR ratio of 1.1. Our study demonstrated the risk of GFR reduction by checking SCr, especially among patients with diabetes, CKD and HF.

Other relevant information from our data was: lowest prescription of preventive hydration before TC (27.75%) and higher intake of biguanide (metformin) on the contrast injection day (6.25%). The European Guidelines to CIN described that 75% of CIN studies reported some form of hydration as a prevention approach.[18] They recommended expansion volume before contrast with saline or bicarbonate solution. Biguanide (metformin) has the possibility of worsening CIN, with an associated increased risk of lactic acidosis. However, there are no direct studies on the subject.[18] Prevention guidelines are based on the expert

consensus about metformin pharmacokinetics and CIN pathophysiology.[4,6,18] In this study, we did not find any association between CIN and the use of metformin or lack of expansion volume (data not shown in the study).

The main strength of the meta-analysis is the large number of patients included (n = 400), resulting in an estimate of the CIN incidence after contrast-enhanced CT. Moreover, we have chosen a logistic model by default for all analyses to cope statistically with patient heterogeneity, resulting in a conservative incidence estimate compared to a fixed effects model.

The limitations of our study are mainly the facts that it was carried out in a single center and the impossibility of monitoring these patients to determine other possible outcomes such as death or dialysis.

Conclusion

Despite the difficulties due to the variability of this population, this study is one of the few prospective publications that have shown the use of intravenous contrast after CT as a variation factor associated with acute kidney injury. This condition is stronger in patients with diabetes and heart failure.

Conflicting interests

The authors declare that they have no conflicting interests.

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