

Computerized Tomography Contrast Induced Nephropathy (CIN) among adult inpatients

Nefropatia induzida por contraste (NIC) em pacientes adultos internados submetidos à tomografia computadorizada por contraste

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Data de submissão: 19/02/2014.

Data de aprovação: 28/08/2014.

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DOI: 10.5935/0101-2800.20140064

ABSTRACT

Introduction: Contrast induced nephropathy (CIN) is one of the complications of the use of intravascular contrast agents, being defined as a reduction of the glomerular filtration rate caused by the iodinated contrast. Most CIN data derive from the cardiovascular literature, which identified as the most consistent risk factors pre-existing chronic renal insufficiency and *diabetes mellitus*. However, these studies limit their conclusions to a more specific patient population. Computerized tomography as a cause of CIN has been studied less often. **Objective:** To report on the incidence of computerized tomography contrast induced nephropathy (CIN) in an inpatient population of a tertiary general hospital, identifying potentially avoidable risk factors. **Methods:** We performed a prospective cohort study with inpatients admitted at a tertiary hospital requiring contrast-induced CT. The primary outcome was the development of CIN, measure by the alteration of serum creatinine or glomerular filtration rate in 48 or 72 hours. Through clinical interview, we verified possible risk factors and preventive measures instituted by the medical team and their association with development of CIN. **Results:** Of a total of 410 patients, 35 (8.5%) developed CIN. There was a positive correlation between CIN and the presence of *diabetes mellitus* (OR = 2.15; 95%CI 1.35-4.06; $p = 0.02$), heart failure (OR = 2.23; 95%CI 1.18-8.8; $p = 0.022$), and renal failure (OR = 3.36; 95%CI 1.57-7.17; $p = 0.002$) **Conclusion:** Incidence of CIN varies according to the population. *Diabetes mellitus*, heart failure and renal failure were independent risk factors for the development of CT-associated CIN. Further studies are needed to better understand and treat CT-associated CIN.

Keywords: renal insufficiency; acute kidney injury; contrast media; hospital mortality; nephrology; inpatients; tomography.

RESUMO

Introdução: Nefropatia induzida por contraste (NIC) é consequência do uso de meios de contraste intravenoso, sendo definida como uma redução da taxa de filtração glomerular. A maioria dos dados de NIC são da literatura cardiovascular, que identificou como fatores de risco insuficiência renal crônica e diabetes. Entretanto, esses estudos limitam suas conclusões a uma população específica de pacientes. Tomografia Computadorizada contrastada como causa de NIC foi menos estudada. **Objetivo:** Reportar incidência de NIC numa população de pacientes internados em hospital terciário submetidos à tomografia computadorizada com contraste, identificando possíveis fatores de risco evitáveis. **Métodos:** Realizamos um estudo de *coorte* prospectivo com pacientes internados em hospital terciário e que necessitaram de tomografia computadorizada com contraste. O desfecho primário foi desenvolvimento de NIC, verificado por meio da variação da creatinina sérica ou taxa de filtração glomerular em 48 ou 72 horas. Em entrevista clínica, verificamos possíveis fatores de risco, assim como medidas preventivas instituídas pela equipe médica e suas possíveis associações com desenvolvimento de NIC. **Resultados:** Do total de 410 pacientes, 35 (8,5%) desenvolveram NIC. Houve correlação positiva entre desenvolvimento de NIC e a presença de *diabetes mellitus* (OR = 2,15; 95%CI 1,35-4,06; $p = 0,02$), insuficiência cardíaca (OR = 2,23; 95%CI 1,18-8,8; $p = 0,022$), e insuficiência renal (OR = 3,36; 95%CI 1,57-7,17; $p = 0,002$). **Conclusão:** A incidência de NIC varia de acordo com a população. Diabetes, insuficiência cardíaca e insuficiência renal foram fatores de risco independentes para o desenvolvimento de NIC. Mais estudos são necessários para melhor entendimento e tratamento da NIC relacionada à tomografia computadorizada.

Palavras-chave: insuficiência renal; lesão renal aguda; meios de contraste; mortalidade hospitalar; nefropatias; pacientes internados; tomografia.

INTRODUCTION

Contrast induced nephropathy (CIN) is one of the most serious consequences of the use of intravascular contrast agents, being defined as a reduction of the glomerular filtration rate caused by the iodinated contrast.¹⁻³ When not prevented, CIN may result in significant morbidity and mortality.⁴⁻¹⁶ Although low osmolarity and iso-osmolarity contrast media have been used for more than half a century, its physiopathologic effects on the kidneys remain largely unknown.¹⁷ Most CIN data derive from the cardiovascular literature, which identified as the most consistent risk factors pre-existing chronic renal insufficiency and *diabetes mellitus*.¹⁸ However, these studies limit their conclusions to a more specific patient population.

Contrast induced nephropathy in computerized tomography (CT) has been studied less often. A recent meta-analysis on the subject found only five clinical trials correlating CIN and computerized tomography, none of them in an inpatient population.¹⁹ These few studies pointed out to diverse incidences and risk factors of CIN, possibly due to differences both in the definition of CIN and in patient characteristics.¹⁹⁻²² The objective of our study is to report on the incidence of computerized tomography CIN in an inpatient population of a tertiary general hospital, identifying potentially avoidable risk factors.

METHODS

We performed a cohort study with inpatients of a tertiary hospital submitted to various regimens of CT with intravenous contrast media. All subjects were at least 18 years old, remained in the hospital for at least 48 hours after the CT, and signed an informed consent. We excluded from the study patients who had been exposed to contrast media in the previous 30 days prior to enrollment, patients who died or were discharged less than 48 hours after the CT, and those who did not sign the informed consent form.

Data were collected from patient interviews, chart reviews, and laboratory exams. The variables accessed were: age, gender, *diabetes mellitus*, hypertension, heart failure, stroke, body mass index (BMI), serum creatinine, glomerular filtration rate (GFR), drug use, more specifically metformin, acetyl salicylic acid (ASA), angiotensin conversion enzyme (ACE) inhibitors, beta blockers, non-steroidal

anti-inflammatory drugs (NSAIDs), and antibiotics, and the adoption of specific CIN preventive measures instituted by the medical team (so far, there are no standard protocols for the prevention of CIN at our institution).

Serum creatinine was obtained before contrast injection and 48hs after the exam. The same contrast media (intravenous Telebrix 30®, Guebert Laboratories, 1650 mOsm/Kg/H₂O) was employed in all studies. We defined CIN as an absolute rise in serum creatinine of at least 0.5 mg/dL or as a relative increase in serum creatinine of at least 25% of the base value, 48hs after the administration of the intravenous contrast.²³ Age was dichotomized in less than 65 years or 65 years of more. The loss of renal function was defined by different methodologies; initially, we considered the classic, most common definition of renal function loss as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² by the Cockcroft-Gault formula or a serum creatinine ≥ 1.5 mg/dL.^{24,25} Ultimately, we have adopted the recommendation from the Kidney Disease Improving Global Outcomes (KDIGO), which defines the loss of renal function using the 2009 Chronic Kidney Disease Epidemiology Collaboration's (CKD-EPI) formula.²⁶ In doing so, additional data were obtained from patients, from family members, and from chart reviews.

Data were entered twice into a Microsoft Excel®, (version 7 for Windows) database by two different data managers, and were ultimately compared, to control for typing errors. Continuous variables were described as means and standard deviation (SD); categorical variables were described as frequencies and percentages. Student's *t* test was used to compare continuous variables, whereas Chi-square (χ^2) and Fisher's exact tests were used for categorical variables and Kappa test. Stepwise Backward logistic regression was used to evaluate the correlation of the variables with the development of CIN. Statistical analysis was performed with the software SPSS® (*Statistical Package for the Social Sciences* v. 17.0 for Windows). We considered as statistically significant a *p* value of less than 5% ($p \leq 0.05$).

RESULTS

From May 2007 to February 2008, we have studied 410 patients, of whom 52% were male, 12.7% were older than 65 years, 80% were caucasian and 19.2% were black. Hypertension was present in 39.5%,

whereas renal failure was seen in 31% (Cockcroft-Gault) and 30.2% (CKD-EPI 2009) of patients. Cancer was present in 30.5%, diabetes in 14.1%, and heart failure in 7.1%. Regarding medications used when CT was performed, 23.3% of the patients were using ACE inhibitors, 17.8% beta-blockers, 15.1% ASA, and 2.2% NSAIDs.

The indications for a CT in our study were: staging of neoplasms (62.2%), evaluation of pulmonary thromboembolism (12%), abdominal pain (5.6%), infectious diseases (4.4%), liver diseases (2.9%), thoracic and abdominal aortic aneurisms (3.6%), neurologic diseases (2%), or other (7.3%). Mean contrast volume during CT was 139.1 ± 31.2 mL. Correcting according to the body's surface area, we obtained a value of 81.0 ± 2.1 mL/m².

In our study, 23% of the patients were treated with intravenous saline before and after the procedure, whereas only 2.5% received bicarbonate. However, there was no significant association between these measures and a reduction in CIN.

Overall, 35 patients (8.5%) developed CIN. There was a positive correlation between CIN and the presence of *diabetes mellitus*, heart failure and renal failure, as shown in Table 1.

TABLE 1 VARIABLES ASSOCIATED WITH THE DEVELOPMENT OF CIN (BACKWARD STEPWISE LOGISTIC REGRESSION)

Variable	Significance	Odds Ratio	95.0% C.I. for EXP(B)	
DM	0.019	2.149	1.135	4.067
Heart failure	0.022	3.23	1.184	8.816
NSAIDs	0.053	5.21	0.978	27.79
Renal failure	0.002	3.36	1.574	7.174
Age \geq 65 years	0.79	0.33	0.096	1.138

Variable(s) entered on step 1: gender, race, hypertension, DM, heart failure, cancer, NSAIDs, betablockers, age 65 or older, BMI, hydration protocol, renal failure.

In comparing the diagnosis of renal failure using the Cockcroft-Gault formula and the 2009 CKD-EPI test, we obtained a value of 0.954 ($p < 0.016$; kappa statistics).

DISCUSSION AND CONCLUSIONS

Current knowledge about the actual magnitude of CIN in CT derives from studies performed in diverse populations, none of them inpatients. In a study of

diagnostic CT for peripheral arterial disease in an ambulatory population, El-Hajjar *et al.*¹ described a 1.75% incidence of CIN. Mitchell *et al.*²¹ described an 11% incidence of CT-associated CIN (with a 2% mortality rate) in emergency room patients. In a cohort of kidney transplant receptors, Ahuja *et al.*²⁷ have reported on a 21.0% incidence of CIN. Lencione *et al.*²⁰ describe an incidence of 2.5% of CIN with inpatients but it was a retrospective study. Our incidence of computerized tomography CIN (8.5%) refers to an inpatient population from a tertiary hospital, which treats a wide range of medical conditions. We did not study ambulatory or emergency care patients, and this has to be taken into account when analyzing our results. We believe that the differences in the incidence of CIN verified across the studies are mainly due to the variability of the patients' clinical conditions, rather than to disparities in the definition criteria of CIN.

The significant risk factors for CT-associated CIN in our study were renal failure, DM, and heart failure. Both renal failure and DM are established as risk factors for CIN in the literature.²⁸ Heart failure, however, is viewed a possible risk factor.^{27,29} The association of heart failure and CIN could be due to aspects peculiar to these patients: low cardiac output and high levels of catecholamines which eventually impair renal perfusion.³⁰

The role of NSAIDs as risk factors for CIN has been recently debated.^{23,31} Although NSAIDs have been listed as possible risk factors for CIN, it is mostly based on physiopathologic assumptions, and there are no consistent evidences to support this association.³⁰ We have recently reported a lack of association between the use of NSAIDs and CIN in a population submitted to cardiac catheterism.²³ Other potential risk factors for CIN, such as multiple myeloma, were not confirmed by clinical studies.³² According to Goldemberg & Matetzky,³³ many of the conditions pointed in the literature as risk factors for CIN were determined by studies that were either controversial or experimental. Although the alpha have been borderline, due to the very low frequency of NSAIDs use in our sample (2.2%), it was not possible to ascertain the actual interaction between these drugs and CIN in this study.

Our study has some limitations that cannot be underestimated. Firstly, most CTs performed in our study were required for the diagnosis or staging of patients with cancer, and this should be taken into

account when generalizing our results. Secondly, we have evaluated exams performed with only one type of contrast media, and we did not assess the impact of agents that are supposedly less nephrotoxic (non-ionic, low-osmolarity agents). Thirdly, although we could not find a significant association between the use of NSAIDs and CIN, few patients were using NSAIDs at the time of the study. Finally, we have excluded from analysis patients with multiple exposures to contrast media previously to enrollment, which could be a risk factor for the development of CIN by itself.

To our knowledge, this is the first prospective study of CT-associated CIN in patients admitted to a tertiary hospital. Further studies are necessary to evaluate risk factors for CT-associated CIN in different patient populations.

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