

## Is There an Association between Non-steroidal Anti-inflammatory Drugs and Contrast Nephropathy?

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### Abstract

**Background:** The association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acute or chronic renal failure is well documented, but evidence of such association between NSAIDs and Contrast-Induced Nephropathies (CIN) is not found in the indexed literature.

**Objective:** To evaluate the possible association between NSAIDs and CIN.

**Methods:** In a cohort study, through clinical interviews of patients that underwent cardiac catheterization, we analyzed the use of NSAIDs and its association with the development of CIN, through alterations in serum creatinine or glomerular filtration rate in 48 or 72 hours.

**Results:** From July 2005 to July 2006, 236 patients were enrolled in the study, of which 29 were later excluded. The incidence of CIN was 10.37% (20 of 207) and 42% of the patients were using NSAIDs until the moment of the evaluation. There was no association between the use of NSAIDs and the development of CIN with OR of 1.293 95% CI (0.46-4.2). The study detected known risk factors for the development of CIN, such as diabetes with OR of 2.77 95%CI (1.05-7.47) and chronic renal failure with OR 3.48 95%CI (1.1-11.07). A protective action of saline solution hydration is also suggested, with OR of 0.166 95%CI (0.03-0.92).

**Conclusion:** Based on the data obtained, we conclude that there was no association between CIN and previous use of NSAIDs, at least with an OR higher than 2.85, which our sample detected. (Arq Bras Cardiol 2010;95(6):726-731)

**Keywords:** Anti-inflammatory agents, non-steroid; kidney diseases/chemically induced; risk factors.

### Introduction

The use of contrast media has increased worldwide, not only for diagnosis, but also for interventional radiology procedures. It has been estimated that in western countries over 6,000 diagnostic and 2,000 therapeutic cardiac catheterizations are performed yearly per million inhabitants<sup>1</sup>. In parallel with these observations, the prevalence of contrast-induced nephropathy (CIN) has also risen<sup>2</sup>. It is currently the third leading cause of hospital-acquired renal failure<sup>3</sup> and is associated with prolonged hospitalization, potential need for renal replacement therapy and increased mortality<sup>4</sup>. The incidence of CIN in the general population has been reported to be less than 2%<sup>5</sup>. However, in high-risk patients, such as those with chronic renal impairment, diabetes mellitus, congestive heart failure and older age, its incidence may reach up to 20-30 %<sup>6,7</sup>.

Many variables have been identified as potential risk factors for the development of CIN, with varying levels of evidence. Preexistent low glomerular filtration rate (GFR) and diabetes mellitus<sup>5,8-10</sup> share the strongest evidence as major risk factors. However, age<sup>11</sup>, gender, contrast medium infused volume<sup>9,11,12</sup> and osmolarity<sup>8,12-18</sup>, use of angiotensin-converting enzyme (ACE) inhibitors<sup>19</sup>, peripheral artery disease and acute myocardial infarction have also been associated with the development of CIN<sup>4,20,21</sup>.

Although there is no clinical proof that non-steroidal anti-inflammatory drugs (NSAIDs) increase the risks of CIN, their well documented nephrotoxicity, both in clinical<sup>22-25</sup> and experimental<sup>26-28</sup> settings suggest a possible association. We approached this issue by studying a cohort of inpatients who underwent cardiac catheterization at a tertiary university hospital, in whom the use of NSAIDs was evaluated as a possible risk factor for the development of CIN.

### Methods

We conducted a prospective, observational cohort study, in which all patients older than eighteen years old, who had been hospitalized to undergo cardiac catheterization at our tertiary

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university hospital from July, 2005 to July, 2006 were asked to participate. Written informed consent was obtained from each patient before enrollment. Patients who had received any intravenous iodinated contrast medium within the previous ten days of the cardiac catheterization were excluded from the study. Additionally, patients receiving any form of renal replacement therapy at the time of the evaluation were also excluded from the study.

The association between the use of NSAIDs and the development of CIN was evaluated through a clinical interview and review of the medical record data. The interview was conducted with every patient soon after cardiac catheterization; patients were questioned about the previous use of specific NSAIDs, including the amount and period of use. Known risk factors for the development of CIN were registered: age over 75 years, male gender, diabetes mellitus, chronic renal failure (serum creatinine over 1.5 mg/dl), dehydration, congestive heart failure, acute heart attack within the last 24 hours, anemia (defined by World Health Organization - WHO criteria), history of peripheral artery disease, osmolarity and volume of the contrast media, the use of an intra-aortic balloon, emergency catheterization and history of hypertension. The use of saline or bicarbonate solutions prescribed by the medical assistants was also registered, since both may have a protective action<sup>6,7,29,30</sup>. We also recorded the use of any other drugs at the time of the cardiac catheterization.

All patients were followed for 72 hours after cardiac catheterization. Serum creatinine was measured before catheterization and repeated 48 and 72 hours after the procedure. A single central laboratory performed all analyses. The primary endpoint was an increase of >0.5 mg/dl (>44  $\mu$ mol/L) or a 25% increase in serum creatinine above baseline levels within 48 or 72 hours after contrast administration<sup>31</sup>.

The study protocol was approved by the bioethics committee of our institution, which is in accordance with the principles stated in the revised Helsinki Declaration.

### Statistical analysis

Sample size was calculated based on an estimated 25% rate of exposure to NSAIDs and on an estimated 15% incidence of CIN. A minimum of 212 subjects would thus be necessary to perceive an odds ratio of three or more, with an alpha error of 5% or less and a statistical power of 80%.

Data were entered on EPIDATE (EPI-INFO) database twice, by two separate investigators in order minimize typing errors; thirty-three mismatches were found and subsequently corrected. Data were analyzed with the Statistical Package for Social Sciences v.12. Analysis of the increase in serum creatinine levels from baseline to those obtained at 48 or at 72 hours after the evaluation was performed with the use of a multiple linear regression, as the distribution of the variables was normal. Categorical or dichotomized data were analyzed by logistic regression in a stepwise backward model.

## Results

Overall, 236 subjects were enrolled in the study. Twenty-nine patients (12.2%) were excluded from the analysis

because they were discharged before 72 hours of follow up. A total of 207 patients were eligible for data analysis. Table 1 shows the descriptive data of our sample. Forty-two percent of the patients (n=87) were using NSAIDs at the time of cardiac catheterization.

### Effect of NSAIDs on serum creatinine concentrations

The crude analysis showed that mean creatinine levels at baseline in the groups with and without documented use of NSAIDs were 1.180 mg/dl and 1.274 mg/dl, respectively ( $p\alpha=0.138$ ); peak creatinine levels at 48 hours were 1.197 mg/dl and 1.359 mg/dl ( $p\alpha=0.02$ ) and at 72 hours were 1.197 mg/dl and 1.357 mg/dl ( $p\alpha=0.046$ ), respectively, which suggests a possible protective action of NSAIDs on serum creatinine levels. There was no linear correlation between use of NSAIDs and the change in serum creatinine levels across time (baseline to 48 and 72 hours).

### Effect of NSAIDs on the development of CIN

The overall incidence of CIN was 10.37% (20 of 207 patients) in our sample. No association between the use of NSAIDs and the development of CIN was found (OR=1.293; 95%CI: 0.416 - 4.02).

### Risk factors for altered creatinine levels and for the development of CIN

We performed a multivariate analysis by multiple linear regression to evaluate risk factors for altered creatinine levels at 48 and 72 hours, including: serum creatinine levels at baseline, patient age, time of NSAIDs use, contrast volume, systolic and diastolic pressure, and hematocrit (all variables

**Table 1 - Risk factors for contrast nephropathy between groups**

Group	Without NAIDs (%)	With NAIDs (%)	P $\alpha$
Male gender	63	42	0.005
Diabetes	10.9	14.8	0.48
Heart failure	20.6	27.9	0.24
Hypertension	85.7	85.2	0.929
Peripheral arterial diseases	32.6	36.1	0.618
Anemia	5.2	3.3	0.542
ACEI	65.7	65.6	0.984
Age over 75 year	16.6	6.6	0.64
AMI	12.7	13.1	0.936
Hyper-osmolar contrast medium	44.7	45.5	0.92
Chronic renal failure	20.2	11.5	0.174
Calcium channel blockers	11.5	9.7	0.695
Saline solution	83.6	80.5	0.588
Bicarbonate solution	13.1	16.7	0.512

ACEI - angiotensin-converting enzyme inhibitor; AMI - acute myocardial infarction.

## Original Article

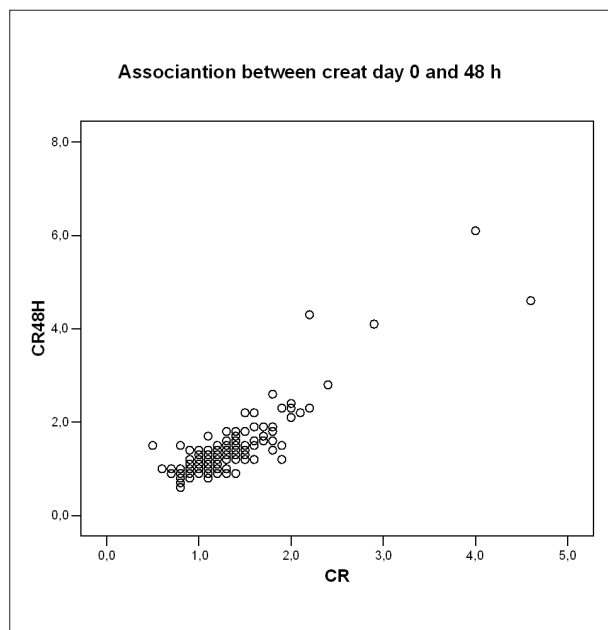
had a normal distribution). A strong positive correlation was found between baseline serum creatinine levels and altered serum creatinine levels at 48 and 72 hours, with respective beta values of 0.781 ( $p\alpha < 0.001$ ) and 0.786 ( $p\alpha < 0.001$ ) (Table 2, Figures 1 and 2).

We also performed a multivariate analysis of risk factors for the development of CIN over 72 hours (Table 3). The most important predictor of CIN in our sample was the presence of chronic renal failure (OR=3.48;  $p\alpha=0.03$ ). Additionally, the presence of diabetes mellitus was a risk factor for the development of CIN (OR=2.77;  $p\alpha=0.04$ ). The use of saline solutions before the cardiac catheterization was a protective factor for the development of CIN (OR=0.166;  $p\alpha=0.04$ ). We also found a borderline association between the use of bicarbonate solutions before the catheterization and the prevention of CIN (OR=0.155;  $p\alpha=0.075$ ) (Table 3).

**Table 2 - Association between CIN and continuous variables**

	Beta coefficients 48 h	P $\alpha$	Beta coefficients 72 h	P $\alpha$
Age	0.103	0.213	0.104	0.352
Time of use (days)	-0.03	0.714	0.167	0.164
Creatinine on day 0	0.781	0.000	0.786	0.000
Hematocrit	0.156	0.061	0.057	0.611
Volume contrast	0.011	0.898	0.044	0.687
Systolic blood pressure	0.238	0.065	0.096	0.578
Diastolic blood pressure	-0.024	0.850	0.044	0.790

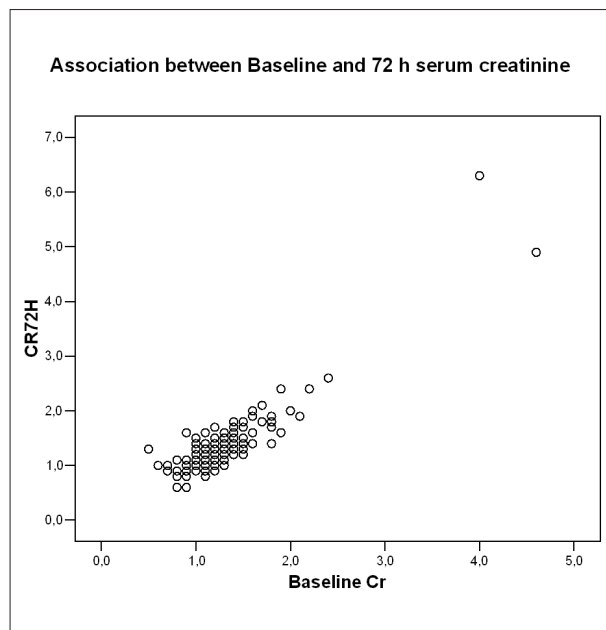
Dependent variable: creatinine 48 h and 72 h.



**Figure 1 - Association between creat day 0 and 48 h.**

## Discussion

Nonsteroidal anti-inflammatory drugs are some of the most frequently prescribed drugs worldwide. A study performed in 1999 estimated that over 18.5 million courses of NSAIDs were prescribed in England and Wales during that year. The estimated cost of these prescriptions was £ 170 million at that time, not considering the eventual need for concomitant gastro-protective agents<sup>32</sup>. A Canadian study suggested that for every dollar spent with NSAIDs, another 0.66 were spent for the treatment of secondary side effects<sup>33</sup>. In the United Kingdom (UK), the annual cost of NSAIDs toxicity in rheumatoid arthritis (RA) patients has been estimated to be £58 million<sup>34</sup>. Moreover, approximately 10,000 hospitalizations and 2,000 deaths occur each year in the UK due to NSAIDs-related side effects in the treatment of musculoskeletal pain<sup>35</sup>. The cyclooxygenase-2 inhibitors (coxibs) may have a superior gastrointestinal safety profile compared to non-selective NSAIDs<sup>36</sup>; however, all kinds of NSAIDs have been



**Figure 2 - Association between baseline and 72 h serum creatinine.**

**Table 3 - Outcomes of logistic regression with stepwise backward model**

Group	OR	95%CI	P $\alpha$
Diabetes	2.77	1.05-7.47	0.045
Age > 75 years	2.368	0.665-8.435	0.183
Chronic renal failure	3.484	1.1-11.07	0.034
Calcium channel blockers	1.988	0.526-7.508	0.311
Saline solution	0.166	0.03-0.92	0.04
Bicarbonate solution	0.155	0.02-1.12	0.075
NSAIDs	1.293	0.416-4.02	0.657

Dependent Variable: Development of CIN 1.

consistently associated with the development of acute or chronic renal failure<sup>22</sup>.

The use of NSAIDs is not clearly associated with an increased risk of CIN in the medical literature. Since these agents are intrinsically nephrotoxic, there could be a synergistic action with contrast agents in the development of CIN. However, this is not always the case. Multiple myeloma (a known cause of renal impairment) was always considered a risk factor for CIN, but recent studies showed that this risk is only increased in myeloma patients with preexisting nephropathy<sup>37</sup>. A previous study about the risks of developing CIN detected only a trend ( $p\alpha=0.07$ ) for the use of NSAIDs<sup>38</sup>.

The percentage of patients using NSAIDs in our study population was high, which is in accordance with the published literature. This could be explained by the fact that we studied inpatients of a tertiary hospital, many of them with multiple co-morbidities. Our sample apparently was consistent with that of other studies, since it had enough power to show a positive association between established risk factors (diabetes, chronic renal failure) and CIN.

The univariate analyses showed an inverse association between the use of NSAIDs and an increase in serum creatinine levels. However, this association did not persist in the multivariate analysis.

The lack of association between the use of NSAIDs and CIN could be explained by a variety of reasons. Cohort studies need more subjects in order to maintain enough power to show a presumed association when there is a lower incidence of events. We found a lower incidence of CIN than we expected and this could be one of the reasons that justify the outcome. Currently, there is a great concern about avoiding CIN in patients submitted to cardiac catheterization. In our study, for instance, we did not find any hypotensive or hypovolemic patients during the evaluation. However, we

can safely estimate that there is no association between the use of NSAIDs and the development of CIN with an OR = 2.85 or greater.

Another possible explanation for our findings is that the renal lesions produced by contrast agents and by NSAIDs are distinct, not necessarily producing a synergistic effect<sup>39</sup>. Whilst the renal impairment secondary to contrast is caused by a direct exposure to the media<sup>1</sup>, NSAIDs lesions are produced in specific physiological settings, such as hypovolemia and hyponatremia<sup>27,29</sup>, in which renal perfusion is largely dependent on the prostaglandin system.

In our study, we found the same protective effect of saline solution described by other observational studies<sup>40</sup>. It is quite possible that the administration of saline to >80% of our patients influenced the low rates of contrast-induced nephropathy. Nevertheless, since no large prospective, randomized trial of deliberate hydration *versus* no intervention for the prevention of CIN has been conducted, we cannot affirm that this effect is really factual. The same can be said about the borderline protective effect of bicarbonate solution in our sample.

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### Study Association

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