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Frequency of acute kidney injury induced by contrast media administration

Frecuencia de lesion renal aguda inducida por medio de contraste

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Abstract

Background: *Acute kidney injury (AKI) related to intravenous (IV) contrast media exposure is a global concern since induced nephrotoxicity is among the main causes of AKI in hospitalized patients after medical procedures such as enhanced computed tomography (CT) scans and percutaneous vascular interventions. This research aims to determine the frequency of AKI after IV contrast media exposure.* **Methods:** *A prospective cohort including 273 patients divided into four groups was performed. Groups I-III were exposed to IV contrast media. Serum creatinine was measured before and after procedures, and the glomerular filtration rate (GFR) was calculated. Univariate, bivariate, and multivariate statistics were used to calculate mean differences and AKI-related risk factors.* **Results:** *Only group one [percutaneous coronary intervention (PCI)] showed statistical changes in GFR after contrast media exposure, and 11.4% of patients in this group developed AKI. No significant differences were observed in the other groups. Multivariate analysis showed no relation between gender, anthropometric characteristics, and comorbidities with AKI development after IV contrast media exposure.* **Conclusion:** *Results reported in the present study showed that IV contrast media exposure has no significant changes in GFR after enhanced CT scans. However, after PCI, significant changes in GFR were observed ($p < 0.05$), including AKI in some patients.*

Keywords: *Acute kidney injury. Intravenous contrast media. Glomerular filtration rate.*

Resumen

Introducción: *La lesión renal aguda (LRA) relacionada con la exposición a medio de contraste intravenoso es un problema de trascendencia global ya que la nefrotoxicidad inducida se encuentra entre las principales causas de LRA en pacientes hospitalizados después de procedimientos médicos como tomografías con administración de contraste e intervenciones vasculares percutáneas. Esta investigación tiene como objetivo determinar la frecuencia de LRA después de la exposición a medios de*

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contraste intravenosos. **Métodos:** *Se realizó una cohorte prospectiva de 273 pacientes divididos en cuatro grupos. Los grupos 1, 2 y 3 fueron expuestos a medio de contraste intravenoso. Se midió la creatinina sérica antes y después de los procedimientos y se calculó la tasa de filtración glomerular (TFG). El análisis estadístico incluyo medidas de tendencia central, análisis bivariado y multivariado para calcular las diferencias de medias y los factores de riesgo relacionados con la LRA.* **Resultados:** *Solo el grupo uno (intervención coronaria percutánea) mostró cambios significativos en la TFG después de la exposición a medios de contraste, y el 11,4% de los pacientes de este grupo desarrollaron LRA. No se observaron diferencias significativas en los otros grupos. El análisis multivariado no mostró relación entre el sexo, las características antropométricas y las comorbilidades con el desarrollo de LRA tras la exposición a medios de contraste intravenosos.* **Conclusión:** *Los resultados en el presente estudio mostraron que la exposición a medio de contraste intravenosos no tiene induce a cambios significativo en la TFG en pacientes sometidos a tomografías computarizadas. Sin embargo, después de la intervención coronaria percutánea, se observaron cambios significativos en la TFG ($p < 0,05$), incluidos casos de LRA, en algunos pacientes.*

Palabras clave: *Lesión renal aguda. Medio de contraste intravenoso. Tasa de filtrado glomerular.*

Background

Acute kidney failure (AKI) is a clinical syndrome characterized by a sudden deterioration of renal function, which leads to a variable degree of alteration of the body's homeostasis. The decrease in diuresis and the increase in the concentration of nitrogenous products of metabolism are its most frequent clinical features[1]. Diagnostic criteria for AKI include an abrupt reduction in renal function (within 48 hours), defined as an absolute increase in serum creatinine equal to or greater than 0.3 mg/dL (≥ 26.4 mmol/L), a percentage increase equal to or greater than 50% (1.5 times the basal level), or a reduction in urine flow[2].

The incidence rate of AKI patients admitted to a hospital ranges from 1 to 13% in all admitted patients but increases to 1.5-25% among critically ill patients. The mortality rate for AKI in ICUs is around 60%[3,4].

Contrast media-induced nephrotoxicity (CIN) consists of a sudden deterioration in kidney function after the recent intravascular administration of a solution containing iodinated contrast media and in the absence of another nephrotoxic event. CIN is the third cause of acute rheumatic fever (12% of cases) in patients admitted to hospital care. CIN has an incidence of 2% in the general population, although, in patients with diabetes mellitus, congestive heart failure, chronic renal failure, and older age, the incidence increases between 20 and 30%. The incidence rate of CIN is around 1,50,000 cases globally, of which 1% require replacement of renal function and hospital admission or prolongation of stay[5]. CIN has been defined as an absolute increase in plasma creatinine of 0.5 mg/dL over its baseline value or a relative increase of 25% in the 48-72 hours after administering a contrast medium in the absence of other demonstrable causes of AKI[6]. The effect of contrast medium on renal tubular cells suggests toxic and ischemic mechanisms[7].

Contrast media induce vasoconstriction in the afferent artery of the glomerulus and renal vascular stasis, causing ischemic injury and cell death in the proximal and distal tubules. Increased blood viscosity further amplifies vasoconstriction, increasing renal medullary hypoxia[8].

The use of IV contrast medium is a frequent practice due to its usefulness as a diagnostic and therapeutic tool in various medical areas of this tertiary care unit. This work aims to determine the frequency of AKI associated with the use of a contrast medium.

Material and methods

A prospective study cohort was carried out at the Western National Medical Center under the Institutional Committee of Ethics' permission (R-2015-1301-106). Inclusion criteria for study subjects were the following: Both genders, older than 18-year-old, and a previous procedure on which patients received IV or intraarterial contrast media (enhanced CT scan or PCI). Patients with acute coronary diseases were excluded from this study. Based on previous therapeutic management, the cohort was divided into four groups. The sample was calculated using Epi-Info™ StatCalc (Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America).

Statistical analysis included measures of central tendency and proportions (population characteristics and biological markers). Serum creatinine and anthropometric data were used to calculate the GFR before contrast media use in all patients. A total of 72 hours after contrast media administration, new serum creatinine was measured to calculate GFR again. Mean differences in

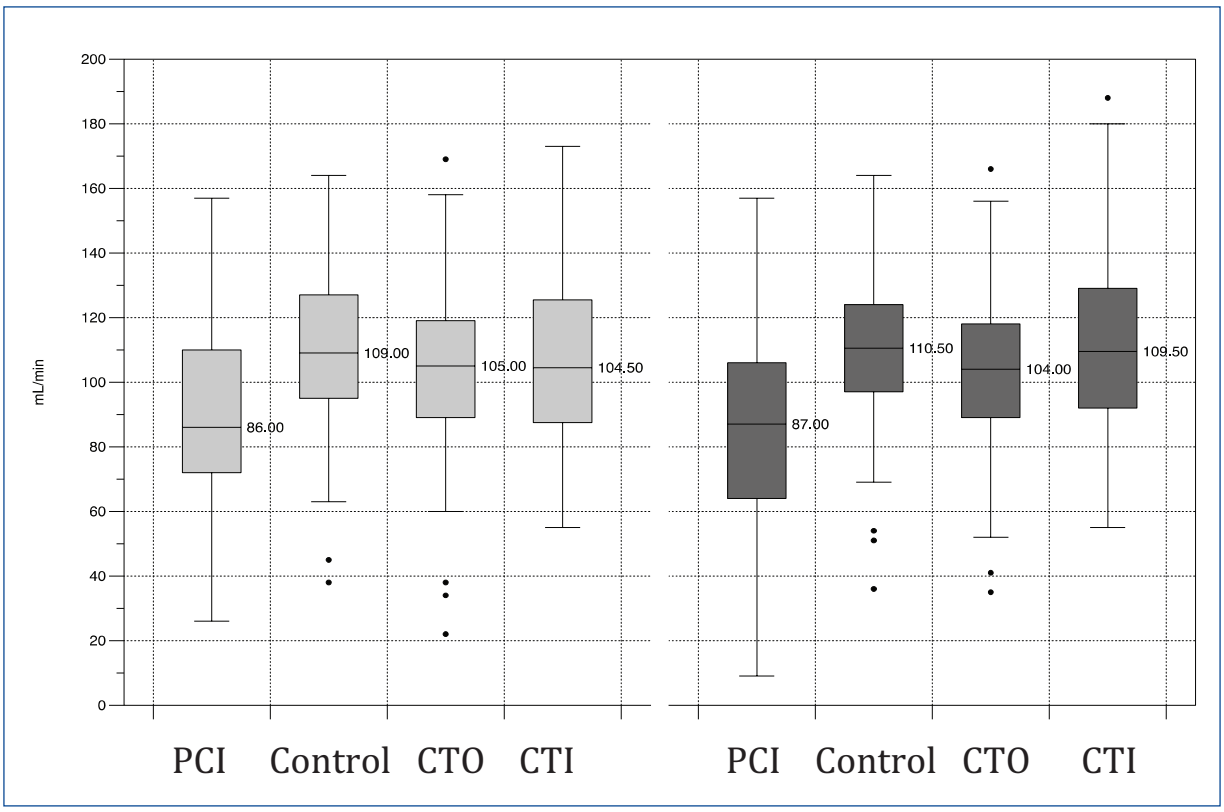

Figure 1. Glomerular filtration rate (GFR) variation before and after IV contrast media administration.

GFR: glomerular filtration rate chronic kidney disease epidemiology collaboration (CKD–EPI) (mL/minute/1.73 m^2). Wilcoxon test before and after PCI group ($p < 0.011$); Wilcoxon test before and after the control group ($p > 0.05$); Wilcoxon test before and after CT scan outpatients (CTO) group ($p < 0.05$); Wilcoxon test before and after CTI group ($p < 0.01$).

serum creatinine and GFR before and after contrast media use were calculated using the Mann–Whitney *U* test ($p < 0.05$). Logistic regression was used to associate independent variables with AKI.

Results

A total of 273 patients (63% males) were included in four groups, as previously mentioned. The mean age and body mass index (BMI) for both groups were 55.4 [standard deviation (SD) 15.8] and 25.9 (SD 4.5), respectively. Basal serum creatinine in the whole sample was 0.79 mg/dL (SD 0.26). The GFR mean was 101.8 mL/minute/1.72 m^2 (SD 26.7). 27.5% of patients had diabetes mellitus type 2 (16.5% managed with metformin).

Before contrast media administration and based on GFR, 70% of studied patients were classified as KDIGO 1. Two patients (0.7%) were classified as Kidney Disease Improving Global Outcomes (KDIGO) 4. The rest of the patients (29.3) were classified as KDIGO 2 and 3. Table 1 describes the characteristics of each one of the four study groups.

The Mann–Whitney *U* test showed significative differences in regard to age groups ($p < 0.05$) except between groups III and IV.

Frequencies for diabetes and hypertension in each group were 51.4, 25, 12.3, and 20, and 61.4, 41.2, 10.8, and 25.7%, respectively.

The frequency for anemia was reported in 11.4, 26.56, 18.5, and 28.6 for groups 1-4, respectively.

Table 2 shows GFR values before and after IV contrast media administration. A significative difference was reported in group I ($p < 0.01$). The other groups did not show significant differences.

After IV contrast media administration, AKI incidence was 12.9/100 patients. No AKI cases were reported in the other groups; therefore, the global incidence was three/100 patients.

Glomerular filtration rate (GFR) variations before and after IV contrast media administration are shown in Figure 1. Significative differences were observed in all groups ($p < 0.05$) except for the control group. Differences observed in both the enhanced CT scan outpatients and CT scan in patient groups were due to

Table 1. Characteristics of study groups

Total sample (n = 273)			
Group 1 PCI	**Group 2 Enhanced CT scan* inpatients**	**Group 3 Enhanced CT scan* outpatients**	**Group 4 Nonenhanced CT scan (control group)**
(n = 70) Age mean (years) = 64.1	(n = 68) Age mean (years) = 57.5	(n = 65) Age mean (years) = 50.5	(n = 70) Age mean (years) = 49.2

*Only IV contrast media administration.

Table 2. GFR values before and after IV contrast media administration

Study groups	GFR mean* (SD) Before IV contrast media application	GFR mean* (SD) After the IV contrast media application	p-value Mann-Whitney *U* test
PCI	88.2 (26.5)	82.9 (31)	$p < 0.01$
CTI	106.7 (25.9)	111.9 (29.7)	$p > 0.05$
CTO	103.2 (25.3)	102.9 /23.6)	$p > 0.05$
Nonenhanced CT scan (control group)	108.5 (23.9)	110.2 (24.4)	$p > 0.05$

*CKD-EPI mL/minute/1.73 m^2.

a rise in GFR reversal to decreasing GFR values in the CT scan inpatients (CTI) group.

Linear regression analysis was used to evaluate the correlation between AKI and some variables such as gender, age, BMI, GFR, diabetes, hypertension, metformin use, anemia, and contrast media volume. No correlation was found between AKI and the previously mentioned variables in the crude model.

Discussion

The obtained results show that only the PCI developed AKI; meanwhile, the other two exposed groups did not have kidney damage based on the GFR. Based on the reported result, it can be assumed that AKI risk is overestimated in patients that undergo enhanced CT scans since GFR changes in both groups (inpatients and outpatients) demonstrated no significant differences ($p > 0.05$).

According to the international literature, AKI is a frequent concern after PCI and other minimally invasive cardiovascular procedures. The main feature is the increasing progressive serum creatinine levels within the first 48–72 hours after contrast media IV administration. Effects on tubular epithelial cells and the release of vasoactive molecules are related to an increased oxidative state that leads to ischemic cell injury[9,10].

Another pathway for damage is the direct effect of toxicity in renal tubular cells and medullary ischemia. Medullary ischemia results in a dysregulation between delivery and oxygen demand[11], resulting in increased oxygen species and decreasing nitric oxide levels, resulting in endothelial and vascular damage. Damage mechanisms related to contrast media direct cytotoxicity are apoptosis, autophagia, and osmotic necrosis and *in vitro* studies have demonstrated increased cell death by apoptosis and autophagia[12]. All previous mechanisms increase serum creatinine levels and decrease renal perfusion[13].

Other variables are assumed to be implicated in AKI development after contrast media exposure. The most frequent risk factors associated with impaired renal function include anemia, diabetes, hypertension, contrast media volume, age (most frequently in the elderly), and other metabolic conditions. In 2018, Molen et al. concluded that there are no specific risk factors to increase AKI risk and that more controlled studies are necessary. The only risk factor depicted by the authors was high osmolarity contrast media[14].

The reported frequency of contrast media-induced AKI has been decreased after definitions consistent with KDIGO guidelines of a rise in serum creatinine ≥ 0.3 mg/dL or a ≥ 50% elevation from the baseline over the hospitalization time[13,15]. The US National Cardiovascular Data Registry, Cath PCI reported 7.1% of cases of contrast media-induced AKI in 2007[13]. The incidence reported in 2015 was 2.3% in 2,000 patients[16].

Previous studies related to contrast-induced nephropathy have focused on populations undergoing coronary angiography in such a way that the vast majority of risk factors and stratification scales, as well as prevention measures, are based on these studies[16,17].

Some other medical procedures on which contrast media is required can induce AKI. However, some authors consider such concerns as an overestimated fact. In several medical facilities, previous to IV contrast media administration, serum creatinine determination is mandatory, which could restrict the use of such diagnostic or therapeutic procedures associated with contrasting media use[18].

A meta-analysis of 28 studies performed by Aycock et al. in 2017[18] reported no differences in kidney damage, need for dialysis, or mortality after enhanced CT scans and non-enhanced CT scans in 1,07,335. Results obtained in the former study are similar to results obtained in the present research since differences between non-enhanced CT scans vs enhanced CT scans were not statistically significant ($p > 0.05$).

This study represents one of the few investigations carried out in our environment focused on identifying risk factors associated with the appearance of AKI. Compared to the studies mentioned in previous paragraphs, where the general frequency for AKI is around 2.3%[16], the one found in this study has been very similar (2.9%). The appearance of AKI only stands out in the group of patients who underwent cardiac catheterization (11.4%). This behavior of CIN is consistent with that observed in other studies, where the incidence is higher in patients who underwent coronary angiography, even though the actual incidence observed in this study is lower than that reported in other published studies.

AKI is a chemically adverse effect after the administration of iodine compounds. The physiopathology effects are due to several factors, including hemodynamic changes such as the reduction of renal perfusion and the toxic effects on tubular cells, which are crucial factors involved in the pathogenesis of IV contrast media-induced AKI[19,20].

After exposure, vasoconstriction is the most crucial cause of ischemia and the decrease of GFR. Medullary ischemia seems to be caused by alterations in renal microcirculation and an increase in oxygen consumption[21]. The modulation of vasoconstriction and vasodilatation is significant in medullary ischemia, so NO and prostaglandins are essential to maintain this balance. When this balance is lost, complications may arise. A study showed that inhibition of NO and prostaglandins in a murine model resulted in higher vasoconstriction after administering contrast media[22]. Osmotic necrosis and vacuolization have been observed in tubular cells, which leads to cell death[23].

On the molecular level, a significant modulation is observed, studies reveal that NO may be downregulated partially by the decrease of the cortical and medullary microvascular blood flow[24], and this correlates with the increase of ROS, which in turn, might increase the levels of urinary 3-nitro-tyrosine, which is a biomarker of nitrogen-free radical species[25,26].

Studies show that CM might induce cell death by autophagy and apoptosis[27]. Mitophagy plays a vital role in the survival of endothelial cells; however, the mechanisms associated with it are not well elucidated yet[28].

Endothelial cells may also be directly damaged by contrast media, reacting to it by shrinking and increasing the oxidation and translocation of HSP60 to the cell membrane[29]. Contrast media have toxic effects on the mitochondria, affecting the enzymatic activity and the membrane potential, which could induce apoptosis[20].

The analysis of subgroups allows us to identify that the group of patients undergoing cardiac catheterization had significant differences with the rest of the groups in different variables. The age distribution was higher in the catheterization group than in the rest of the study groups. The prevalence of diabetes mellitus and arterial hypertension was higher in this same group of patients. This same group's mean and median initial GFRs were significantly lower compared to the rest of the study groups. GFR after medium contrast exposure only showed a significant change from the baseline in the coronary intervention and contrast-enhanced tomography groups. Although the change shows to be statistically significant, the actual clinical change tends to be insignificant in each of the groups.

The obtained results are comparable with international reports. Evidence between contrast media exposure and some medical conditions as determinants for AKI is debatable, and more scientific evidence is necessary. Controlled studies, including hydration, nephrotoxic drug exposure, physiologic creatinine variations, and others, are necessary to put over the table the real effects between contrast media exposure and AKI development.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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