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ORIGINAL RESEARCH

Contrast-induced nephropathy in patients undergoing percutaneous coronary intervention

Nefropatía inducida por medio de contraste en angiografías coronarias

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Key words: Contrast-induced nephropathy, acute kidney injury, coronary angiography, Mexico.

Palabras clave: *Nefropatía inducida por contraste, lesión renal aguda, angiografía coronaria, México.*

ABSTRACT

Introduction: Contrast-induced nephropathy (CIN) is defined as the impairment of renal function and is measured as either a 25% increase in serum creatinine (SCr) from baseline or 0.5 mg/dL increase in absolute value, within 48-72 hours of intravenous contrast administration. **Objectives:** Objectives were to calculate incidence of CIN and to describe the clinical and periprocedural risk factors for patients receiving contrast media. Secondary objective was to compare mortality between group 1 and group 2. **Material and methods:** In a retrospective, observational, descriptive cohort study, patients who were admitted to the hospital for diagnostic and/or therapeutic coronary angiography between January 2014 to September 2015, the serum creatinine and glomerular filtration rate (GFR) prior to angiography and 72 hours later was measured. **Results:** 70 patients were included, of which 14.2% developed CIN. The leading risk factors for developing AKI were: age > 65 years (OR 12.6, CI95 1.6-105.9, p = 0.03); the presence of anemia (OR 7.5, CI95 1.8-31.2, p = 0.006); and procedural time more than 90 minutes (OR 16, CI95 3.1-85.3, p = 0.001). Higher mortality was observed in the NIC group (30% vs. 1.6%, p = 0.004). **Conclusions:** The incidence is higher than in the literature review. The leading associated risk factors were age > 65, anemia and procedural time > 90 minutes. The development of CIN carries a higher mortality.

RESUMEN

Introducción: *Se define como nefropatía inducida por medio de contraste (NIC) a un aumento absoluto de la creatinina sérica mayor a 0.5 mg/dL o un aumento relativo de la creatinina sérica mayor al 25%, 48-72 horas posteriores a la exposición al medio de contraste en comparación con los niveles previos después de haber excluido otras causas de lesión renal aguda (LRA).* ***Objetivo:*** *Determinar la incidencia de NIC y analizar los factores de riesgo asociados en los pacientes que desarrollaron LRA posterior a un procedimiento de angiografía coronaria. Se determinó mortalidad entre ambos grupos como objetivo secundario.* ***Material y métodos:*** *Se realizó un estudio de cohortes, observacional, descriptivo y retroelectivo. Se analizaron los pacientes que ingresaron en enero de 2014 a septiembre de 2015, para angiografía coronaria diagnostica y/o terapéutica. Se determinó la creatinina sérica y tasa de filtración glomerular (TFG) previa a la angiografía y 72 horas; además se identificaron los factores de riesgo asociados al desarrollo de NIC.* ***Resultados:*** *Se incluyeron 70 pacientes, de los cuales 14.2% desarrollaron NIC. Los factores de riesgo predictores más importantes para desarrollar FRA fueron la edad > 65 años (OR 12.6; IC95 1.6-105.9, p = 0.03); la presencia de anemia (OR 7.5; IC95 1.8-31.2, p = 0.006); y una duración de procedimiento mayor a 90 minutos (OR 16; IC95 3.1-85.3, p = 0.001). Se observó mayor mortalidad en el grupo NIC (30 versus 1.6%, p = 0.004).* ***Conclusiones:*** *La incidencia reportada es mayor que la literatura. Los factores de riesgo asociados más importantes fueron la edad > 65, anemia y procedimiento > 90 minutos. El desarrollo de NIC conlleva una mayor mortalidad.*

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INTRODUCTION

Contrast-induced nephropathy (CIN) is defined as the impairment of renal function and is measured as either a 25% increase in serum creatinine (SCr) from baseline or 0.5 mg/dL increase in absolute value, within 48-72 hours of intravenous contrast administration.[1-3]

CIN is an important cause of acute kidney injury (AKI) in hospitalized patients being

reported as the third most common cause of kidney injury in patients who underwent interventional radiologic procedures.[4] However, the incidence of CIN is less than 2%[5] although, in patients with chronic kidney disease (CKD) the incidence is more than 12%, as well as in patients who developed an acute coronary syndrome (ACS) and underwent an urgent percutaneous coronary intervention (PCI).[6] Even more, is also associated with excess mortality and longer hospital stay.[7,8]

The pathophysiology of CIN *(Figure 1)* is based on contrast media (CM) which act on distinct anatomic sites within the kidney and exert adverse effects via multiple mechanisms. They cause a direct cytotoxic effect on the renal proximal tubular cells, enhance cellular damage by reactive oxygen species,

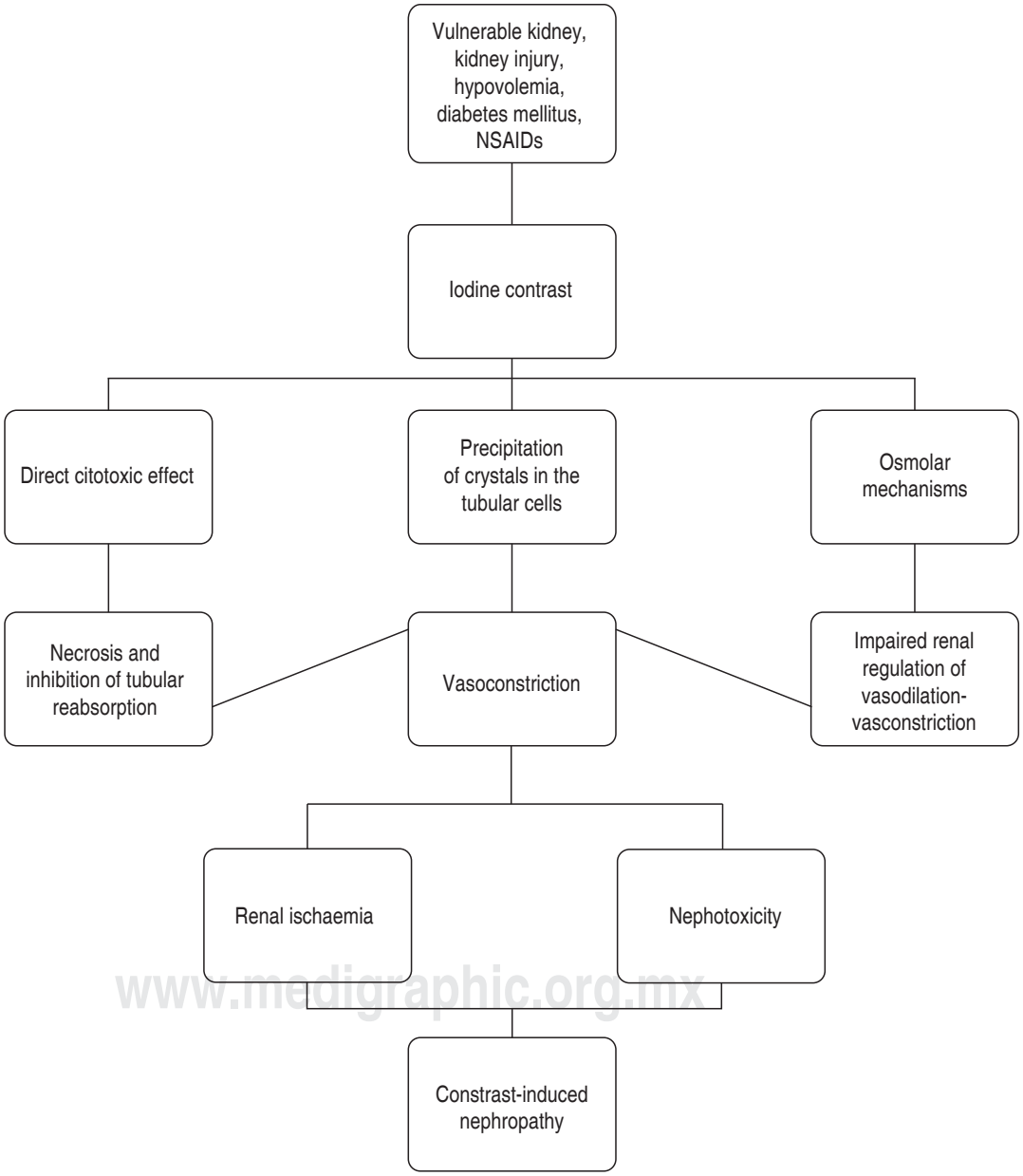

Figure 1.

Contrast-induced nephropathy physiopathology.

Adapted from Fernández-Cimadevilla OC et al. Med Clin (Barc). 2011; 137 (2): 84-90.

and increase resistance to renal blood flow. They also exacerbate renal vasoconstriction, particularly in the deeper portions of the outer medulla.[9,10]

CIN is normally a transient process, with renal functions reverting to the baseline within 7-14 days of contrast administration.[9] Less than one-third patients develop some degree of residual renal impairment, and renal replacement therapy is required in less than 1% of patients, with a slightly higher incidence in patients with underlying AKI raising the mortality up to 17%, compared with just 3.9% in patients who don't develop AKI.[11-13] Preexisting renal impairment and diabetes mellitus appears to be primary risk factors for CIN.[13]

The presence of dehydration, anemia, congestive heart failure (New York Heart Association (NYHA) III-IV), age > 70 years, gout, the use of nephrotoxic and NSAID drugs, all these increase the risk for AKI. Patients undergoing primary PCI for myocardial infarction got some extra risk factors to develop CIN (hemodynamic instability, severe transient hypotension, use of intra-aortic balloon counterpulsation, undergoing emergency procedures and arterial contrast administration).[14-16]

The leading predictor for CIN is a preexistent kidney injury, which increases more than 20 folds the risk for developing CIN, when glomerular filtration rate (GFR) is < 45 mL/min/1.73 m2. Furthermore, it has been found that not only decreased in the glomerular filtration rate predicts the appearance of contrast nephropathy; proteinuria plus a decreased GFR increases the incidence.[17]

There is few evidence in the literature review that evaluates the incidence and the risk factors that are associated with contrast media use in patients with ischemic cardiomyopathy that underwent a diagnostic or therapeutic PCI.

The objective of this study was to calculate the incidence of CIN and to describe the clinical and periprocedural risk factors for patients receiving contrast media and as a secondary objective was to compare mortality between patients who developed CIN and those who not. Our hypothesis is that the incidence and the risk factors of CIN is equal than the literature.

MATERIAL AND METHODS

Study design

In a cohort, observational, descriptive and retrospective study, patients who were admitted to the hospital for diagnostic and/or therapeutic PCI between January 2014 to September 2015 and the serum creatinine and GFR were measured previous to the angiography (day 0) and 72 hours after contrast administration were included in the study. The GFR was calculated by the Modification Diet in Renal Disease (MDRD) formula. Risk factors to develop CIN and protective factors to prevent CIN were included in the study.

Inclusion criteria

1. Patients older than 18 years old who were admitted to the hospital Christus Muguerza Alta Especialidad, in Monterrey, Nuevo Leon, Mexico and underwent to PCI and had a serum creatinine measured prior to contrast administration, as well as 72 hours after the procedure.

Exclusion criteria

1. Patients who were in renal replacement therapy (peritoneal dialysis or hemodialysis).
2. Patients who did not complete a minimum 24-hours stay at the hospital.
3. Patients who did not have serum creatinine levels at the day of angiography (day 0) and 72 hours after the procedure.
4. Patients who had a previous AKI episode.

Elimination criteria

1. Patients who died during coronary angiography.
2. Patients who underwent procedures in which amount of contrast used was not reported.

Statistics

Microsoft Excel and Medcalc® were used. Continuous variables were expressed with median and standard deviation, and qualita-

tive variables as percentage. Continuous variables were analyzed with student's t test and categorical variables with χ^2 test. Multivariate analysis was performed by logistic regression of the variables and results were expressed with odds ratio with confidence intervals of 95% and were expressed as a significant result when $p < 0.05$. It was calculated a given sample size of 64 patients to accomplish a significance of 0.05 and a beta error of 20%.

Conceptual definitions

Contrast-induced nephropathy: the impairment of renal function and is measured as either a 25% increase in serum creatinine (SCr) from baseline or 0.5 mg/dL increase in absolute value, within 48-72 hours of intravenous contrast administration.

Anemia: it was defined using the World Health Organization criteria as hemoglobin < 13 g/dL in men and < 12 g/dL in women.

Hypotension: blood pressure less than 90/60 mmHg.

Nephroprotective actions: hydratation, N-acetylcisteine or sodium bicarbonate use.

Ethical considerations

Because it was an observational study of non-intervention, there are no ethical problems associated with their implementation. There is no risk to humans. The confidentiality of the identity and personal data of patients was safe

RESULTS

During the period covered from January 2014 to September 2015, one hundred and four coronary angiographies were performed, of them 34 patients were excluded because did not meet the inclusion criteria. Seventy patients met the inclusion criteria; 10 patients developed AKI, with an incidence in our hospital of 14.2%. From these patients during the hospital stay, 3 (30%) died, and 1 (10%) required hemodialysis after angiography.

In patients who developed AKI *(Table I)*, a predominance of males was observed, 7 out of 10 patients were men (70%), with a median age of 74.2 (± 8.10) years, however, in patients who did not develop AKI the mean age was lower at 59.18 (± 14.61) ($p = 0.0024$).

Among the demographic variables, patients with decreased renal function, 30% had diabetes mellitus type 2, 60% had high arterial hypertension and 10% had congestive heart failure. On admission, 6 (60%) patients with AKI had anemia compared with 10 (16.6%) patients without AKI ($p = 0.0089$).

The average baseline creatinine was similar in both groups with an average about 1 mg/dL, however showed difference at 72 hours; in the CIN group the mean was 1.87 (± 0.69) mg/dL, compared with 0.97 (± 0.29) in the group without CIN ($p < 0.0001$). This correlated with a reduced GFR at 72 hours in patients with AKI (42.88 [± 21.30] versus 90.92 [± 36.34], $p < 0.0001$).

It was found that intra-aortic balloon counterpulsation use (40% versus 3.33%, $p = 0.0013$) and the presence of periprocedural hypotension (40% versus 10% $p = 0.043$) was greater in patients with CIN, however in the multivariate analysis no significant difference was observed.

No difference was found in the type and amount of contrast media used between both groups, nevertheless patients who had a longer angiography time were more likely to develop AKI (112 min. [± 36.41] versus 71.86 min. [± 28.10], $p = 0.0002$).

By using the area under the curve analysis, time longer than 90 minutes showed a higher risk for development of AKI with an 80% sensibility and an 86.4% specificity, positive likelihood ratio of 6 (2.9-12.3) and a negative likelihood ratio of 0.52 (0.1-1.9). No difference was found in patients underwent to urgent procedure for develop CIN.

Also the area under the curve analysis for the amount of contrast media showed that more than 200 mL of contrast media was associated with further risk of development of CIN, with a sensibility of 80%, a specificity of 38%, a positive likelihood ratio of 1.33 (0.9-1.9) and a negative likelihood ratio of 0.52 (0.1-1.9).

Significant difference in mortality was found, being greater in those patients who developed CIN (30% versus 1.6%, $p = 0.004$). A 30-fold increase in mortality was documented in patients who developed CIN (OR 29.57; 95CI 2.7-323.7, $p = 0.005$).

Table I. Baseline demographic characteristics.

Characteristics		AKI (n = 10) n	AKI (n = 10) %	No AKI (n = 60) n	No AKI (n = 60) %	p
Men		7	70	52	87	0.38
	Age (mean)	74.2		59.18		0.0024
	SD	± 8.10		± 14.61		
DM		3	30	23	38.33	0.88
Hypertension		6	60	20	33.33	0.21
HF		1	10	4	6.66	0.78
Anemia		6	60	10	16.6	0.0088
BMI	Mean	28.60		27.78		0.63
	SD	± 7.95		± 4.22		
Pre-procedure hypotension		4	40	6	10	0.043
Baseline creatinine	Mean	1.07		0.98		0.49
	SD	± 0.42		± 0.33		
72-hours creatinine	Mean	1.87		0.97		<0.0001
	SD	± 0.69		± 0.29		
Baseline GFR	Mean	75.07		92.99		0.19
	SD	± 38.89		± 39.57		
72 hours-GFR	Mean	42.88		90.92		0.0001
	SD	± 21.30		± 36.34		
Nephroprotective actions		2	20	31	51.66	0.13
Urgency procedure		6	60	24	40	0.4
IABC		4	40	2	3.33	0.0013
Type of contrast media used	Ioversol	4	40	11	18.33	0.26
IABC	Iobitridol	0	0	3	5	0.91
Type of contrast media used	Iodixanol	5	50	43	71.66	0.32
	Iohexol	1	10	3	5	0.91
Quantity of contrast media (mL)	Mean	191		200.03		0.72
	SD	± 52.63		± 75.60		
Iodine grams	Mean	59.57		62		0.75
	SD	± 17.50		± 23.47		
Number of occluded-vessels	Mean	1.2		1.2		0.64
	SD	± 0.87		± 0.75		
Number of endoprothesis	Mean	1		1		0.55
	SD	± 1		± 0.88		
Procedure time (minutes)	Mean	112		71.86		0.0002
	SD	± 36.41		± 28.10		
Death		3	30	1	1.6	0.004
Renal replacement therapy		1	10	0	0	0.3

AKI: Acute kidney injury, SD = Standard deviation, DM = Diabetes mellitus, HF = Heart failure, BMI = Body mass index, GFR = Glomerular filtration rate, IABC = Intra-aortic balloon counterpulsation.

A multivariate analysis was performed *(Table II)*, showing a strong association to develop CIN in patients with age greater than 65 years (OR 12.6; 95CI 1.6-105.9, p = 0.03); anemia onset prior to the procedure (OR 7.5; 95CI 1.8-31.2, p = 0.006); and a median procedure time more than 90 minutes (OR 16; 95CI 3.1-85.3, p = 0.001).

DISCUSSION

The major finding of this study was that the incidence of CIN media was 14.2%, higher than reported in similar studies such as that of Rihal et al;[11] showing that it is a common complication, even in patients with normal renal function. It is important the prevention and early diagnosis of this entity, because in our study it is associated with an increased mortality in hospitalized patients as Bouzas-Mosquera[6] had documented.

It is important to remember that although we had a high incidence of AKI and most patients in this study were at high risk, there are other causes besides the use of contrast media that could influence the decrease in renal function, as a atheroembolism, drug toxicity or hemodynamic changes; all these factors making it harder to differentiate the true cause of AKI, as Newhouse reported.[18]

In this study, it was documented that patients who developed CIN by definition were of older, had anemia or hypotension before the procedure, had the necessity for intra-aortic balloon counterpulsation for hemodynamic support and a longer angiography time. In the multivariate analysis used for risk factors, it was found that the angiography time greater than 90 minutes, followed by age and the presence of anemia, all these risk factors were the most strongly associated with CIN, that results are similar to other studies.

In the study population, no statistically significant difference in the use of nephroprotective measures between both groups was documented; nevertheless, the quantity of patients in which these measures were used was low, possibly creating a bias in our results.[19,20]

As for weaknesses of this study we should emphasize that it is a retrospective study, with a small sample, single-center, where there is not influenced therapeutic measures, the cause for renal failure was not fully investigated, and it was not established that death was secondary to renal failure or has been a contributing factor.

This study is relevant because it is a rare entity described in our medical practice, leading to high morbidity and increases in-hospital costs. There are increasingly patients undergoing PCI due to ischemic heart disease, so it is necessary to stratify patients at high risk and carry out early preventive measures.

Table II. Multivariate analysis for development of contrast-induced nephropathy.

	Multivariate analysis		
Parameter	OR	CI95%	p
Age	12.6	1.6 - 105.9	0.03
DM	0.11	0.01 - 1.21	0.07
HTN	6.71	0.83 - 54.48	0.07
Cardiopathy	1.1	.1 - 150	0.99
Anemia	7.5	1.8 - 31.2	0.006
IABC	10.41	0.93 - 116.6	0.06
Hypotension	3.41	0.42 - 27.56	0.25
HF	0.54	0.01 - 40.2	0.78
Obesity	1.52	0.24 - 9.56	0.65
Contrast media amount	0.26	0.0181 - 3.82	0.33
Nephroprotection	0.09	0.0076 - 1.17	0.06
Urgency procedure	1.68	0.19 - 14.69	0.64
Procedure duration	16	3.1 - 85.3	0.001

DM = Diabetes mellitus, HTN = Hypertension, IABC = Intra-aortic balloon counterpulsation, HF = Heart failure.

CONCLUSIONS

The reported incidence was higher than that mentioned in the literature. The most important risk factors were age > 65 years old, anemia and patients who underwent PCI procedures longer than 90 minutes. The early detection of risk factors and the development of the NIC is encourage as the present of this entity leads to increased mortality.

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