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PROPHYLAXIS OF CONTRAST-INDUCED NEPHROPATHY IN HIGH RISK PATIENTS WITH NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

PROFILAXIS DE LA NEFROPATÍA INDUCIDA POR CONTRASTE EN PACIENTES DE ALTO RIESGO CON SÍNDROME CORONARIO AGUDO SIN ELEVACIÓN DEL SEGMENTO ST

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ABSTRACT

Introduction and objectives: The effectiveness of the administration of isotonic saline solution and N-acetylcysteine shows different results in the prevention of iodine contrast nephropathy. Our objective was to assess the potential effectiveness of this combined strategy in patients at high risk for contrast-induced nephropathy, who were admitted in our center for percutaneous coronary intervention due to non-ST-segment elevation acute coronary syndrome. ***Method:*** This strategy was applied in the patients mentioned, with at least one risk factor for developing contrast-induced nephropathy: over 80 years, diabetes mellitus, baseline creatinine greater than 1.5 mg/dl or high volume of contrast (greater than 400 ml). The protocol was applied for 12 months (patients that received the prevention protocol) and compared with similar patients in the previous 12 months who received no prophylaxis. ***Results:*** A total of 30 patients (24%) developed contrast-induced nephropathy. The percentage was significantly higher in the group that did not receive prophylaxis: 35.9% vs. 11.5% (p=0.003). ***Conclusions:*** The combination of N-acetylcysteine orally and parenteral hydration in high-risk patients with acute coronary syndrome without ST elevation could be beneficial to avoid the appearance of contrast-induced nephropathy.

Key words: Coronary intervention, iodine contrast medium, contrast-induced nephropathy

RESUMEN

Introducción y objetivos: La eficacia de la administración conjunta de suero salino isotónico y N-acetilcisteína presenta resultados dispares en la prevención de la nefropatía por contraste yodado. Nuestro objetivo fue valorar la posible eficacia de esta estrategia combinada en pacientes con alto riesgo de desarrollar nefropatía inducida por contraste, ingresados y sometidos a intervencionismo coronario percutáneo por síndrome coronario agudo sin elevación del segmento ST en

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nuestro centro. ***Método:*** Se aplicó esta estrategia en los pacientes referidos, con al menos un factor de alto riesgo para desarrollar la nefropatía inducida por contraste: mayores de 80 años, diabetes mellitus, creatinina basal mayor de 1,5 mg/dl o alto volumen de contraste (mayor de 400 ml). El protocolo se aplicó durante 12 meses (pacientes que recibieron el protocolo de prevención) y se comparó con similares pacientes en los 12 meses previos que no recibieron profilaxis. ***Resultados:*** Un total de 30 pacientes (24 %) desarrollaron nefropatía inducida por contraste. El porcentaje fue significativamente mayor en el grupo que no recibió profilaxis: 35,9 % *vs.* 11,5 % (p=0.003). ***Conclusiones:*** La combinación de N-acetilcisteína por vía oral e hidratación parenteral en pacientes de alto riesgo, con síndrome coronario agudo sin elevación de ST, podría ser beneficiosa para evitar la aparición de la nefropatía inducida por contraste.

Palabras clave: Intervencionismo coronario, contraste yodado, nefropatía por contraste

INTRODUCTION

The use of iodinated contrast agents to perform cardiovascular diagnostic and therapeutic techniques has increased over recent decades. Currently, contrast-induced nephropathy (CIN) is the third leading cause of in-hospital acute renal failure, and although in most cases it is mild with later gradual recovery, it reaches a mortality of 14%. The incidence of CIN in the general population ranges from 0.6 to 2.3%, but in high risk patients the incidence may be up to 50%, according to recent studies. This group includes patients with any of the following characteristics: over 75 years, previous renal failure, history of diabetes mellitus, anemia or heart failure, or those relating to the interventionism (use of large volumes of contrast, sustained hypotension or use of intra-aortic balloon counterpulsation).

Various preventive measures in order to prevent the occurrence of this complication have been studied. Adequate periprocedural hydration has consistently demonstrated its effectiveness. The use of N-acetylcysteine in the literature presents contradictory results, and recently a large trial has shown no clinical benefit. However, the possible benefit of combined use of these two measures (hydration along with administration of N-acetylcysteine), especially in patients at very high risk, is not sufficiently proved in the literature.

Our aim was to assess the potential effectiveness of this combined strategy in hospitalized patients at high risk of developing CIN, and undergoing percutaneous coronary intervention (PCI) for non-ST-segment elevation acute coronary syndrome (NSTE-ACS) in the Clinical University Hospital "Lozano Blesa" in Zaragoza, Spain.

METHOD

During the years 2010-2011 and as a project to improve the health care quality, the implementation of a protocol for the prevention of CIN after cardiac catheterization was introduced. It consisted on the periprocedural administration of 1000 ml of saline in 12 hours and 1200 mg/12h of N-acetylcysteine orally for 2 days. The study was conducted over 2 years: data were collected prospectively during the year of implementation of the prophylaxis protocol and compared with a retrospective data collection from the year before the implementation of this protocol.

All patients admitted to the Coronary Care Unit of the Clinical University Hospital of Zaragoza diagnosed with NSTE-ACS, who underwent cardiac catheterization within 24-48 hours and had at least one of the following high risk for developing CIN were included: over 80 years, baseline creatinine greater than 1.5 mg / dl, history of diabetes mellitus or use of more than 400 ml of contrast during PCI. Patients who required intravenous inotropic use, intra-aortic balloon counterpulsation or mechanical ventilation and those with oligo-anuria or anuria for 24 hours before the procedure, or were on dialysis programs were excluded.

Data regarding age, sex, history of hypertension, dyslipidemia, diabetes mellitus and smoking, and peak levels of creatine phosphokinase (CK) and troponin I, were obtained from their medical records. The number of vessels with severe coronary disease, the number of lesions treated and the volume of contrast administered were collected from the Interventional Cardiology Unit database.

Laboratory parameters (serum creatinine and clearance) were determined on the patient's arrival at hospital and 48 hours after cardiac catheterization. Creatinine clearance was estimated using the Cockcroft-Gault formula.

In all cases the angiographic contrast material used was iobitridol, a hydro-soluble, nonionic, and low osmolarity contrast medium.

Patients were divided into two groups depending on the application of the administration protocol of CIN prophylaxis. The primary purpose of the study was the occurrence of CIN, defined as an increase in creatinine value of 0.5 mg / dl or 25% compared to baseline creatinine at 48 hours after the procedure.

Statistical analysis was performed using SPSS 19. Continuous variables were expressed as mean ± standard deviation and qualitative variables as percentages. Continuous variables following a normal distribution, according to the Kolmogorov-Smirnov test, were analyzed using the "Student's *t*-distribution" for independent samples. The binary and categorical variables were analyzed using the chi-square and ANOVA tests, respectively. The alpha statistical significance level was set at 0.05. The hazard ratio was calculated with a confidence interval of 95% and the number of patients needed to treat was calculated as the inverse of absolute risk.

RESULTS

For 24 months, 125 patients were included in the study: 61 in the prophylaxis protocol group (N-acetylcysteine along with hydration with saline solution), and 64 out of the protocol, collected during the 12 months prior to application.

Table 1 shows the baseline characteristics of the two groups, with similar epidemiological characteristics. Baseline creatinine values were higher in the group subjected to the protocol (1.11 ± 0.51 mg / dl vs. 1.45 ± 0.71 mg / dl).

Table 2 shows the characteristics of coronary interventionism in each group: the density and distribution of coronary disease, and its treatment was similar in both groups, although infarct size was slightly higher in patients not subjected to prophylaxis (TnI: 19.8 ± 17.6 ng / ml vs. 13.9 ± 14.4 ng / ml, p = 0.04). It is worth noticing the greater increase in creatinine after the procedure in patients who received no prophylaxis versus those who received it (0.36 ± 0.68 mg / dl vs. 0.11 ± 0.69 mg / dl; 0.05).

Table 3 shows the summary of the indications for CIN prophylaxis, which shows a higher percentage of patients undergoing high volume of contrast in the treated group (30% vs. 48.3%, p = 0.04).

A total of 30 patients (24%) developed CIN. The rate of CIN was significantly higher in the group that did not receive CIN prophylaxis: 35.9% (23/64) vs. 11.5% (7/61) (p = 0.003), which acted as a protective factor for its occurrence with a relative risk of 0.32 (CI 95% 0.15 to 0.69). The number of patients needed to treat to prevent a CIN was 4 (95% CI 3 to 10).

Table 1. Baseline Characteristics.

Variables	Control Group (n=64)	Prophylaxis Group CIN (n=61)	
Age (years)	69,7 ± 10,4	69 ± 16,1	NS
Sex (% males)	82,8	80,3	NS
Body mass index (kg/m^2)	28,8 ± 3,8	28,4 ± 5	NS
High blood pressure (%)	65,6	72,8	NS
Diabetes mellitus (%)	51,6	42,6	NS
Lipid disorder (%)	51,6	64	NS
Smoking (%)	15,6	26,2	NS
Basal creatinine (mg/dl)	1,11 ± 0,51	1,45 ± 0,71	0.002

NS: Non significant.

Table 2. Procedure related characteristics.

Variables	Control Group (n=64)	Prophylaxis Group CIN (n=61)	
1 vessel disease (%)	26,8	44,3	NS
2 vessel disease (%)	16,1	11,5	NS
3 vessel disease (%)	57,1	44,3	NS
LMCA disease (%)	7,8	5	NS
Target lesions	2,1 ± 0,8	1,8 ± 0,8	0.04
Contraste volume (ml)	302 ± 166	318 ± 136	NS
Creatinine after PCI (mg/dl)	1,47 ± 1	1,57 ± 1	NS
Creatinina increase (mg/dl)	0,36 ± 0,68	0,11 ± 0,69	0.05
Highest troponin I level (ng/ml)	19,8 ± 17,6	13,9 ± 14,4	0.04
Highest Creatin-fosfoquinase	757 ± 666	585 ± 438	NS

PCI: Percutaneous coronary interventionism
NS: Non significant
LMCA: Left main coronary artery

Table 3. Indications for contrast-induced nephropathy prophylaxis.

Factores de riesgo	Control Group (n=64)	Prophylaxis Group CIN (n=61)	
Age > 80 years (%)	25	26,2	NS
Diabetes mellitus (%)	51,6	42,6	NS
Basal creatinine > 1,5 mg/dl (%)	22	53,1	0.01
Contrast needed > 400 ml	30	48,3	0.04

NS: Non significant.

DISCUSSION

In our center, the implementation of the protocol of hydration along with N-acetylcysteine in patients with NSTE-ACS at high risk of developing CIN was effective to reduce its incidence. It was decided to use high doses of N-acetylcysteine as the superiority of the 1200 mg dose compared to the 600 mg twice daily had been previously noted.

Many studies have assessed the ability of N-acetylcysteine to prevent CIN. In the work of Tepel et al. and the APART study, prophylactic administration of N-acetylcysteine along with parenteral hydration, was superior to hydration alone in preventing CIN in patients with elevated baseline serum creatinine (2% vs. 21% and 8% vs. 45% respectively). Recently, several studies have reported similar results. However, we can find many contradictory works. Briguori et al. failed to demonstrate the benefit of N-acetylcysteine with hydration compared to hydration alone in 183 patients. Similarly, intravenous administration of N-acetylcysteine in 487 patients with impaired renal function was not effective in preventing CIN in the study of Webb et al. Several factors have been attributed to this disparity of results, but heterogeneity in the methodology of the studies is considered the main one. Many studies only included patients with renal failure without other risk factors from those described for the development of CIN. The multicenter, randomized, placebo-controlled ACT study also failed to demonstrate the protective role of N-acetylcysteine. 2308 patients with at least one risk factor for development of CIN were included and randomized to high doses of N-acetylcysteine 1200 mg (twice daily) before and after the procedure or placebo. The incidence of CIN was similar in both groups 12.7%

(p = 0.97). The limits defined for patients at risk were: age over 70 years (lower than in our sample) and contrast volume greater than 140 ml, much lower than the chosen one and possibly further from the reality of multivessel coronary artery disease treatment in a single procedure.

The hypothesis of this research suggests that the lack of benefit described in some studies may be due to the lack of high-risk patients in the treated groups, so that if the benefit existed only in these, it would be diluted in the total number of patients. That is why it was decided to analyze data from patients at very high risk. Similarly, those with NSTE-ACS were assessed, because they are high risk by definition, admitted to an intensive care unit, and allowing access to a baseline and post-procedure homogeneous analysis. The stringent criteria for high risk (older than 80 years, history of diabetes mellitus, significant renal failure or more than 400 ml of volume of contrast administered during the procedure) resulted in a casuistic that was lower than expected by the NSTE-ACS epidemiology, which did not allow proper randomization and it was possibly the cause of baseline differences between the 2 groups. However, this fact supports our hypothesis, so that although patients who received prophylaxis had an initial profile of higher risks (higher percentage of renal failure and high volume of contrast), they had lower incidence of CIN than the control group.

CONCLUSIONS

Our study shows, with its limitations of a small casuistic, that in patients who are hospitalized and undergoing PCI for NSTE-ACS at high risk of developing CIN, the combined use of parenteral hydration with isotonic saline solution and N-acetylcysteine could be beneficial for its prevention.

Conflict of interest

The authors state that there was no conflict of interest at the time of writing this manuscript.

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