RISK FACTORS FOR CONTRAST-INDUCED NEPHROPATHY AFTER CORONARY ANGIOGRAPHY

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Abstract

Contrast-induced nephropathy (CIN) has become a significant source of hospital morbidity and mortality with the increasing use of iodinated contrast media in interventional procedures. The current understanding of the disease suggests a multifactorial aetiology and many important issues unresolved about the pathogenesis and the prophylactic strategies.

The purpose of this study was to determine risk factors for CIN pathogenesis after coronary angiography.

We retrospectively studied patients undergoing cardiac catheterization from a cardiology clinic from January 2009 to June 2010. All hospitalized patients who had serum creatinine measured one day before and 48 and 72 hours after the procedure were included. Two subgroups were compared in terms of potential risk factors for contrast nephropathy: group A - patients with CIN and group B – patients without CIN.

CIN was defined as an increase in serum creatinine by either ≥0.5 mg/dL or by ≥25% from baseline within the first 48 hours after contrast administration.

We found no statistically significant differences between groups regarding gender, presence of hypertension or diabetes mellitus, cardiac ejection fraction, medical treatment before and after exposure, the type and the amount of contrast medium. In patients who developed CIN age was significantly higher (p= 0.01) and haemoglobin was lower (p= 0.0047). CIN was significantly associated with hypotension (p = 0.0015), loop diuretics use (p=0.04) and a low glomerular filtration rate (p=0.04).

The reduction of glomerular filtration rate, loop diuretics use, anaemia, hypotension and older age were the main risk factors for contrast induced renal failure.

Rezumat

Nefropatia de contrast reprezintă o importantă sursă de morbiditate şi mortalitate la pacienţii spitalizaţi. Cunoştinţele actuale sugerează o etiologie multifactorială, ceea ce face ca numeroase aspecte legate de patogeneza bolii şi posibilităţile terapeutice şi profilactice să fie încă neclare.

Studiul de faţă şi-a propus evaluarea factorilor implicaţi în patogeneza nefropatiei de contrast la pacienţi ce au fost supuşi angiografiei coronariene.

Au fost studiaţi retrospectiv pacienţii cu cateterism cardiac efectuat în Clinica de Cardiologie din Târgu-Mureş în perioada ianuarie 2009 – iunie 2010. Au fost incluşi în studiu toţi pacienţii la care valorile parametrilor de retenţie azotată au fost monitorizaţi cu 24 ore înainte şi la 48, respectiv 72 ore după administrarea substanţei de contrast.

Nefropatia de contrast a fost definită ca fiind o creştere a creatininei serice cu peste 0.5 mg/dl sau peste 25% faţă de valoarea bazală la 48 ore după administrarea substanței de contrast.

Posibilii factori de risc pentru nefropatia de contrast au fost studiaţi comparativ la două grupuri: A – care au dezvoltat nefropatie de contrast (35 pacienţi) şi B – fără nefropatie de contrast (50 pacienţi).

Nu au fost înregistrate diferenţe statistic semnificative între grupuri în ceea ce priveşte sexul pacienţilor, prezenţa hipertensiunii arteriale, diabetului zaharat, tipul şi cantitatea mediului de contrast.

La pacienţii cu nefropatie de contrast am demonstrat valori mai mici ale ratei de filtrare glomerulară (p=0,04) şi hemoglobinei (p= 0,0047), episoade de hipotensiune (p = 0,0015) şi administrarea mai frecventă a diureticelor de ansă (p=0,04) şi vârste mai crescute comparativ cu pacienţii fără nefropatie de contrast (p=0,01).

Scăderea ratei de filtrare glomerulară, anemia, hipotensiunea, utilizarea de diuretice de ansă şi vârsta înaintată au fost principalii factori de risc pentru nefropatia de contrast la pacienţii studiaţi.

Keywords: contrast-induced nephropathy, coronary angiography, risk factors.

Introduction

Contrast-induced nephropathy (CIN) has received increasing attention in the past few years as has been shown to represent a clinical situation associated with a significant risk of morbidity and death [32]. Widespread practice of investigations using contrast and increased addressability of elderly patients to these investigations led to a sharp increase of interest for CIN.

Many studies have attempted to correctly define the main aspects of the aetiology and pathogenesis of contrast nephropathy in order to impose effective prevention strategies. Multiple determinants are described, from medical history, drugs and procedural factors. Even if the list of risk factors and prophylactic measures is updated every day, there is still much to know on this subject.

In this context, this paper aims to study the main risk factors for contrast nephropathy in a population of patients with suspected coronary lesions.

Materials and Methods

Medical records of the Department of Cardiology of the University of Medicine and Pharmacy Târgu Mureș from January 2009 to June 2010 were retrospectively reviewed to identify all patients undergoing angiographic procedures. The study has been accepted by the local ethics committee.

We included in the study patients for whom serum creatinine levels were available 24 hours before and 24, 48, 72 hours or more after procedure.

Eighty-five patients met these criteria.

Patients were divided into two groups: Group A - patients who developed contrast nephropathy, group B - patients who did not develope contrast nephropathy.

Contrast nephropathy was defined as an acute relative increase in serum creatinine (Cr) by 25% over baseline or an absolute increase of 0.5 mg/dL within 24 hours after intravenous administration of contrast [3, 21, 28].

None of the patients was on regular haemodialysis; hydration protocols before and after angiographies were not standardized and varied from patient to patient.

The following parameters were analysed in all patients:

- sex, age, height, weight, the need for investigation as an emergency or not, blood pressure, ejection fraction;
- the reason for hospitalization, associated diseases (noting particularly those diseases considered to be risk factors for contrast nephropathy: diabetes mellitus, hypertension, multiple myeloma, etc.);
- haemoglobin, total cholesterol, serum triglycerides, uric acid, serum potassium, serum creatinine before the procedure and their evolution after 24 hours of contrast administration;
- the administration of oral antidiabetic agents, lipid lowering agents, diuretics, nonsteroidal anti-inflammatory drugs, oral or parenteral hydration, administration of drugs for preventing contrast nephropathy, the type and the dose of contrast medium ioversol and iomeprol;
- clinical outcomes anuria, haemodialysis, death, etc.

The abbreviated MDRD (Modification of Diet in Renal Disease) equation was used to estimate glomerular filtration rate (eGFR).

Statistical data processing was performed using GraphPad Prism version 4.01 for Windows. Continuous variables were expressed as mean ± standard deviation (SD). Comparison between groups was made with Student t-test. The results presented in the contingency tables were assessed with chi-square test [7, 25].

Results and Discussion

Of the 3462 patients admitted in the hospital, a total of 2204 have undergone as investigation with contrast media. A total of 35 patients developed contrast nephropathy: Group A - 13 women (37.14%) and 22 men (62.85%). Group B consisted of 50 patients of which 27 were women (54.00%).

The mean age of CIN group was 67.17 ± 1.68 years and the proportion of patients with diabetes mellitus (a condition that increased the risk of contrast nephropathy) was lower in this group (34.28% *versus* 48%).

Demographic, clinical, hemodynamic characteristics for the group with and without contrast nephropathy are presented in Table I.

Table I

Comparative analysis of demographic, clinical and hemodynamic parameters for the patients with and without CIN

Characteristics and risk factors	Contrast nephropathy group (N=35)	Without contrast nephropathy (N=50)	p
Age (years)	67.17 ± 1.68	60.94 ± 1.70	0.01
Women (no/%)	13 (37.14%)	14 (28.00%)	0.484
Serum creatinine (mmol/L)	128.50 ± 44.72	114.8 ± 49.78	0.19
Systolic blood pressure (mmHg)	120.0 ± 3.51	125.1 ± 3.29	0.30
Diastolic blood pressure (mmHg)	71.18 ± 1.95	74.14 ± 1.54	0.23
Haemoglobin (g/dL)	11.64 ± 0.34	13.03 ± 0.32	0.0047
Total cholesterol (mmol/L)	4.49 ± 1.15	4.30 ± 1.49	0.85
Serum triglycerides (mmol/L)	2.02 ± 2.8	1.81 ± 1.63	0.72
Angiotensin converting enzyme inhibitors (no)	27 (77.11%)	39 (78.00%)	0.94
Oral antidiabetics (no/%)	5 (14.28%)	10 (20.00%)	0.65
Loop diuretics (no/%)	18 (51.42%)	14 (28.00%)	0.04
Parenteral hydration before and after contrast (no/%)	3 (8.57%)	9 (18.00%)	0.34
Acetylcysteine prophylaxis (no/%)	6 (17.14%)	4 (8.00%)	0.30
eGFR (MDRD) (mL/min/1.73mp)	54.61 ± 4.73	67.06 ± 3.99	0.04
Diabetes mellitus (no/%)	12 (34.28%)	24 (48.00%)	0.43
Iomeprol *vs* Ioversol (Contrast medium)	17 (48.57%) / 18	29 (58.00%) / 21	0.50
Hypotension (no/%)	15 (42.85%)	4 (8.00%)	0.0015
Contrast substance volume (mL)	171.5 ± 11.53	166.5 ± 13.58	0.79
Contrast substance volume below 100 mL	13 (37.14%)	26 (52.00%)	0,19
Contrast substance volume greater or equal with 300 mL	4 (11.42%)	10 (20.00%)	0.37
Ejection fraction (%)	46.67 ± 2.197	47.77 ± 1.607	0.68

MDRD (Modification of Diet in Renal Disease); eGFR (estimate Glomerular Filtration Rate)

Age of patients was statistically significant higher in the group with contrast nephropathy.

In the group with contrast nephropathy glomerular filtration rate values were significantly lower (p=0.0475).

Haemoglobin levels were statistically significant lower in patients with contrast nephropathy (p= 0.0047).

In contrast nephropathy group 15 patients experienced hypotension before and after contrast substance administration. Statistical analysis has shown a significant difference between groups (p = 0.0015).

The use of loop diuretics was a risk factor for contrast nephropathy development (p= 0.04) in our study.

We could not demonstrate a link between oral antidiabetics, nonsteroidal antiinflamators or angiotensin converting enzyme (ACE) inhibitors administration and the development of contrast nephropathy in our patients.

Oral acetylcysteine (ACC) was administered to prevent contrast nephropathy in 6 patients in group A and 4 patients in group B, with no statistically significant differences between groups (p = 0.3087).

Iomeprol and ioversol were used as contrast media.

6 deaths during hospitalization were recorded for group A. Oliguria was present in only one patient with CIN. Post procedural haemodialysis was applied to one patient in group A.

The major findings of this study are that age, low glomerular filtration rate, low haemoglobin values and hypotension are risk factors for contrast induced nephropathy.

Contrast nephropathy is an important cause of iatrogenic acute renal dysfunction. Its incidence in the general population is between 1 and 6% in hospitalized patients, but can be higher in patients at risk [2, 3, 4, 24].

The impact of a transient rise of serum creatinine remains uncertain; previous studies have shown that the situation is associated with increased hospital length of stay, higher dead rates and is a predictor of future cardiovascular events [30].

Our study did not allow such observations given the retrospective nature and lack of follow-up data of patients after discharge. It should be noted that depending on the lesions found on coronary angiography, patients were discharged in the period 47-72 hours after exploration. In this setting, post procedure serum creatinine determination was performed only when clinically indicated.

Previous studies have shown that pre-existing renal impairment is an independent predictor of the occurrence of CIN [1]. A study on more than

7500 catheterised patients showed that 22.4% of those who had creatinine values between 2 and 2.9 mg/dL respectively 30.6% of those with serum creatinine levels above 3 mg/dl developed CIN [30].

In studied patients the levels estimates of creatinine clearance were statistically significant lower in patients with CIN, results being consistent with the literature.

Our data differ from previous results showing an increased risk of development of CIN in diabetes patients [6, 34] even if the percentage of diabetics in the CIN group was higher than 50% (65.71%).

Gender may be a risk factor for contrast-induced nephropathy, with hydration offering less protection in women [11]. More, female gender appears to be a marker of worse 1-year mortality after CIN in patients without baseline CRF [14].

In a study that showed a higher incidence of CIN in women, Mueller et al concluded that the significantly higher incidence of CN after percutaneous coronary interventions (PCI) in women seemed largely due to their less favourable baseline characteristics, including lower GFR and higher incidence of arterial hypertension, rather than to female sex itself [26].

In our patients we could not demonstrate that women are more likely to develop nephropathy after administration of contrast medium.

Hypotension appears to be another factor suggestive of an increased risk of CIN in our patients.

There are other authors who recognize hypotension (a systolic blood pressure of 80 mmHg or inotropic support) as a risk factor for CIN. Dangas et al showed that periprocedural hypotension episodes are independent predictors of CIN in patients with chronic kidney disease [8].

Serum haemoglobin levels were statistically significant lower in the group with CIN, which argues for a possible involvement of anaemia as a risk factor in the development of contrast nephropathy. A deterioration of the renal vasculature in patients with anaemia seems a plausible mechanism to explain the more frequent occurrence of contrast nephropathy in this category of patients.

From this perspective our results are consistent with those of literature. Previous studies show that each 3% decrease in haematocrit levels increases the probability of CIN with 30% and 26% if patients have previous impaired renal function [20, 27].

Administration of loop diuretics was a risk factor for nephropathy in our patients, which is also reflected in the literature [18].

Several efficient prevention methods for CIN have been reported of which hydration the most important is [10, 35].

In the absence of statistically significant differences between groups in our patients we cannot support a prophylactic role for parenteral hydration. Our results can be explained by the lack of use of parenteral hydration protocol (hydration was performed by the cardiologist depending on the clinical status of patient).

Also, we cannot support the role of acetylcysteine (ACC) prophylaxis, although in patients at risk (diabetics, etc.) acetylcysteine was administered at doses of 2 x 600 mg/24 hours precontrast and postcontrast medium administration for 24 hours.

Due to its antioxidant and vasodilator effects, acetylcysteine has been proposed as prophylactic therapy. On this subject literature provides conflicting results; some authors supporting its role in prophylaxis alone or in combination with hydration protocol [9, 17. 33] but others do not [5, 12]. Conflicting results have been explained in part by the following factors: negative studies are generally seen in patients with low risk of developing CIN, statistical errors due to small size of study groups lots and large differences between studies on the mode of administration and dose of acetylcysteine.

Several recent studies show that prophylaxis with theophylline reduces the incidence of CIN in patients with moderate or high risk (0% *vs*. 8.8%), making it an important factor in reducing the incidence of CIN [22].

In our study patients, administration of theophylline was very low, possibly in the context of coronary disease, with no significant differences in the administration of theophylline in patients with and without contrast nephropathy. The literature results on this subject are controversial, some authors claiming no role in the prevention of CIN [13].

Statin administration is beneficial in diabetes but was not a protective factor for CIN, although there are studies in favour of this hypothesis [15, 16].

We could not demonstrate that angiotensin-converting-enzyme (ACE) inhibitors have a role in the pathogenesis of CIN, although some studies claim that renin-angiotensin-aldosterone system blockade before administration of contrast often leads to CIN within 72 h [19, 36].

Although there is no clinical evidence that nonsteroidal anti-inflammatory drugs increase the risk of contrast nephropathy [29] avoiding these drugs is required for all clinical guidelines as a prophylactic measure against contrast nephropathy. Our study does not support the involvement of nonsteroidal anti-inflamators in development of CIN.

Also, we could not demonstrate a link between oral antidiabetics and the development of contrast nephropathy in our patients. The small number

of cases in each category may be an explanation for the difference between our results and literature.

Several studies recognized congestive heart failure and left ventricle systolic disfunction as prognostic factors of CIN. Rosenstock J.L. et al showed in a group of patients with chronic kidney disease that only a cardiac ejection fraction of less than 40% was significantly associated with CIN [31].

Rihal et al. showed that low ejection fraction (less than 49%) and advanced congestive heart failure New York Heart Association (NYHA III or IV) are independent risk factors for contrast nephropathy and the risk is further increased by administration of ACE inhibitors, diuretics and aspirin [30].

In our study ejection fraction was not a risk factor for contrast nephropathy but should be noted that in none of the groups were recorded values of ejection fraction below 30%, and the percentage of patients with ejection fraction of 30% was 5% in contrast nephropathy group and 10% in the group without contrast nephropathy.

The dose of contrast medium is a recognized risk factor; some researchers introduce this parameter in risk prediction equations [23].

In this study we do not demonstrate a possible influence of the contrast agent (type of substance, dose) for the development of nephropathy.

Coronary artery investigations were performed with ioversol and iomeprol, low-osmolar non-ionic monomers.

No significant differences were observed regarding the occurrence of contrast nephropathy even when the study was performed for patients who received low doses of contrast medium (below 100 mL), or high doses of contrast (more than 300 mL).

We have not found in the literature clinical studies which compare the two substances. The authors explain the lack of differences in the generation of contrast nephropathy on the basis of similar physiochemical characteristics.

In interpreting our data some limitation must be considered: the retrospective nature of the study, small sample size, very wide case mix of diseases, lack of a uniformity regarding prophylactic measures.

Conclusions

The major finding of this study is that, among a population which underwent cardiac catheterization procedures, the main predictors for the occurrence of CIN were a low glomerular filtration rate, age, low haemoglobin values and the administration of loop diuretics. Our results support the importance of measuring renal function before performing

investigations with contrast medium, especially in the elderly. It is also necessary to apply preventive measures especially in patients who experienced episodes of hypotension before and after exploration and in patients with anaemia.

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