CONTRAST-INDUCED NEPHROPATHY (CIN): A RAPID OVERVIEW FOR RISK ASSESSMENT AND PREVENTION.

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ABSTRACT

In recent years, the number of contrastographic exams has increased considerably, compared to an increase in the complications related to this type of interventional approach. A number of specialists (interventional radiologists, cardiologists, vascular surgeons, cardiac surgeons, etc.) have to deal with complications related to the procedure or contrast medium (CM) used. With regard to the latter, contrast induced nephropathy (CIN) is commonly defined as an increase in serum creatinine (sCr) concentration of 0.5 mg/dL or 25% above baseline within 48 h of CM administration. It is the third most common cause of hospital-acquired renal failure, with an incidence rate that varies from 1 to 25% depending on patient comorbidities. It carries with it a lifelong dialysis therapy risk of 0.5 - 2%. CIN is a condition that can affect anyone subjected to a contrastographic exam, although there are groups at increased risk. The purpose of this article is to describe and analyze the methods used for CIN management, and detail the risk factors associated, with particular emphasis on score systems created to categorise patients according to CIN risk after procedure. The aim is also to create an easy and quick tool to guide doctors presented with a patient facing an injection of CM for diagnostic or therapeutic purposes.

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1. Introduction

Cotton and collaborators were first to describe a case of kidney injury induced by radiocontrast injection (1), and in recent decades the rate of this iatrogenic reaction has increased considerably, in relation to the growing number of contrastographic studies in patients with multiple risk factors. Although there is no consensus in literature, contrast induced nephropathy (CIN) is commonly defined as an increase in serum creatinine (sCr) concentration of 0.5mg/dL or 25% above baseline within 48 h of contrast administration (2); it is currently described as the third most common cause of hospital-acquired renal failure (3), with an incidence rate that varies from 1 to 25% (4) depending on patient comorbidities (5). Although only 0.5-2% of patients with CIN require dialysis, this condition results in a high short and long term mortality rate (6). The aim of this brief report is to review the main predictors of CIN and prognostic and therapeutic paradigms proposed, in order to offer a quick and useful tool for managing this very common and potentially dangerous iatrogenic condition.

2. Risk factors

Even though predisposing conditions exist, all patients are at risk of CIN. The two most important risk factors are pre-existing kidney disease and diabetes mellitus with chronic kidney disease (7-9), assessed by an estimated Glomerular Filtration Rate (eGFR) < 60ml/min per 1.73m² or a sCr > 1.5 mg/dL in accordance with National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease (10). Surprisingly, diabetes mellitus with normal kidney function is not considered a significant risk factor. Other risk factors are listed in Table I, in accordance with the classification proposed by Chang and co-workers (11), in which there are patient-related risk factors (unmodifiable) and modifiable or partially modifiable risk factors; these are accompanied by procedure-related risk factors. As noted, it is important to assess renal,
cardiac and metabolic function in preparation for contrast administration. The nephrotoxic drugs should be stopped within 24-48 hours of the procedure, although there are studies that allow the continuation in patients without kidney disease (12).

Regarding the contrast media (CM), the two parameters to consider are the type and the volume used during the procedure. Low-osmolar CMs (LOCM, i.e. iomeprol, metrizamide, iopamidol and more), have a lower risk of CIN compared to high-osmolar CMs (HOCM, ie diatrizoate, metrizoate and lothalamate) (13). The current Guidelines of the American College of Cardiology / American Heart Association recommend the use of either IOCMs or LOCMs rather than iohexol and ioxaglate (LOCM-type) in patients with renal impairment undergoing angiography (14). The dose of CM used must be as low as possible. Cigarroa and collaborators have shown an increase in probability of CIN of 30% for each 100 ml of CM used beyond the limits (15). Liu and colleagues have demonstrated that a ratio of volume of contrast media to estimated glomerular filtration rate (V/eGFR > 2.39) is a significant and independent predictor of CIN in patients undergoing angiography with acute ST-segment elevation myocardial infarction (STEMI) (16).

3. CIN predicting scores

Given the vastness of risk factors, some studies have proposed a simplified methodology for predicting the risk of CIN. Mehran and co-workers have developed and validated a risk scoring system to predict the risk of CIN and dialysis in a cohort of 8357 patients undergoing percutaneous coronary intervention (PCI) (18). They were divided into a development group (DG, 5571 patients) and a validation group (VG, 2786 patients).

Table 1 - CIN risk factors

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
<th>Procedure-related risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>Pre-existing kidney disease</td>
</tr>
<tr>
<td>Hyponatremia (&lt;35 g/L)</td>
<td>Diabetes with chronic kidney</td>
</tr>
<tr>
<td>Poor heart function or</td>
<td>Iodinated vs. non-iodinated CM</td>
</tr>
<tr>
<td>Hypodynamic instability</td>
<td>Age &gt; 75 y</td>
</tr>
<tr>
<td>Procedural intravascular</td>
<td>High-osmolar CM</td>
</tr>
<tr>
<td>balloon pump or intravenous</td>
<td>High-osmolarity CM</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Multiple CM injections within</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
</tr>
</tbody>
</table>

Table 2 - CIN risk scores index

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>865</td>
<td>5571</td>
<td>688</td>
<td>2047</td>
</tr>
<tr>
<td>Number of variables</td>
<td>14</td>
<td>14</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>CK Dose (mg/L)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Pre-existing CKD</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metformin FV</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urgent/Emergency procedure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IAPB CHF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CRF (mg/dL)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CRF (mg/dL)</td>
<td>2</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>CRF (mg/dL)</td>
<td>1</td>
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<td>1</td>
</tr>
<tr>
<td>CRF (mg/dL)</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>CRF (mg/dL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2 - CIN risk scores index

- CFK: Cardiac Function Killip; BMI: Body Mass Index; IAPB: Intra Aortic Pump Balloon; PVD: Peripheral Vascular Disease; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; eGFR: estimated Glomerular Filtration Rate (ml/min 1.73 m²); sCr: serum Creatinine; PCI: Percutaneous Coronary Intervention; CHF: Chronic Heart Failure; CrCl: Creatinine Clearance; AUC: Area Under Curve. Using serum creatinine as a criterion for renal function; *using estimated glomerular filtration rate as a criterion for renal function; †in derivation cohort.
CIN occurred in 13.1% of DG patients and 13.9% of VG patients. A univariate analysis showed that chronic kidney disease, congestive heart failure (CHF, New York Heart Association functional classification III/IV and/or history of pulmonary oedema) and hypotension (systolic blood pressure<80 mmHg for at least 1 hour requiring inotropic support with medications or intra-aortic balloon pump (IABP) within 24 hours periprocedurally) were more strongly associated with the development of CIN (OR 2.89, 2.68 and 2.36, respectively, p <.0001). A multivariate analysis showed that hypotension, IABP use and CHF were the main risk factors for CIN (using sCr as a criterion for renal function OR 2.54, 2.44 and 2.25 respectively, p <.0001; using eGFR as a criterion for renal function 2.68, 2.55 and 2.70 respectively, p <.0001). Among the risk factors for CIN, the most significant were chosen and weighted according to their ORs. In addition, significant increases in rates of one-year mortality were observed for each risk class in both DG and VG patients: low risk 1.9% and 2.0%, moderate risk 5.5% and 5.7%, high risk 15.5% and 13.5%, very high risk 31.2% and 33.3%, respectively. Mehran risk score was further endorsed as an effective method for predicting CIN in patients with acute coronary syndrome who underwent coronary angiography in another study 10-years later (19). Moreover, a study including 509 consecutive patients treated with elective or urgent PCI (20), replicated subsequently in 2882 patients (21), selected a five variable risk score. In this case, CIN developed in 10.2% of patients. In a multivariate analysis, pre-existing renal disease, metformin use, previous PCI procedures, presence of peripheral arterial disease and contrast volume ≥300 mL were identified as independent and significant predictors of CIN. In patients with a score >3, CIN developed in 83% of cases. Moreover, a risk >2 was associated with a higher incidence of cardiac death, major adverse cardiovascular events (MACE) and re-hospitalizations for heart attack 1 year later. Other studies have tried to delineate risk score systems to identify patients at increased risk of CIN (22-24). Table II summarizes the main features of scores resulting from the literature.

4. Management to prevent CIN

The management of CIN consists of three phases: pre-procedural, intra-procedural and post-procedural. In addition, the pharmacological measures taken can be preventive (before the procedure or in the immediate post procedural time) or therapeutic (when CIN is already diagnosed). In this brief communication only preventive measures will be discussed, leaving the therapeutic management of CIN to specialists.

Hydration

The best way to prevent the occurrence of CIN is pre- and post-procedural hydration. Although there are no convincing results about the method of administration (intravenous or oral), several studies have recommended that it be given intravenously, if possible. CIN prevention is more effective with isotonic saline than hypotonic saline (25), preferably sodium bicarbonate (26). An Italian REMEDIAL trial compared three CIN prevention strategies in 393 patients undergoing coronary or peripheral angiography, with sCr between 2.0 mg/dL and 8 mg/dL and/or an eGFR <40 mL/min/1.73m². About a third of patients were treated with saline plus N-acetylcysteine (NAC), a third with bicarbonates plus NAC, another third with saline, NAC and ascorbic acid. An increase of sCr ≥25% after the exam was recorded in 9.9%, 1.9% and 10.3% (p = 0.010) in the three groups, respectively, causing the authors to conclude that the combined strategy of volume supplementation with sodium bicarbonate solution and NAC was superior (27). A review of current literature recommends that isotonic saline administration should be started at a rate of ≥1-1.5mL/kg/h 3-12h before and 6-12h after contrast media exposure, while sodium bicarbonate should be administered at a rate of 3mL/kg/h 1h before and 1mL/kg/h 6h after contrast media exposure (28). The Canadian Association of Radiologists consensus guidelines for prevention of CIN update (29), published in 2014, recommend:

- For inpatients, 0.9% saline solution at 1 mL/kg/h for 12 hours before the procedure and 12 hours after the procedure.
- For outpatients, isotonic saline or sodium bicarbonate solution at 3 mL/kg/h, a minimum of 1 hour before the procedure and 6 hours after the procedure.

The benefit of these recommendations is that they also offer the possibility of prompt management for patients that come from home or other facilities, or patients in which the decision to carry out the contrastographic examination is taken quickly or when the examination needs to be carried out in an emergency.

N-acetylcysteine (NAC)

Although there are many meta-analysis on the use of NAC in the prevention of CIN, the data published to date remain controversial. Pattharanitima and colleagues, after a systematic review of the literature and meta-analysis comparing the efficacy of NAC and placebo, concluded that due to very low toxicity, low cost, and potential benefits of NAC, it remains commonly used for the prophylaxis of CIN, recommending its use at a dose of 600mg twice daily on the day before and day of the procedures in patients at risk (28).

Other pharmacological approaches, although not disappointing in some studies, have not achieved significant results in the prevention of CIN (28).

5. Protocols

Although there are many articles that describe the characteristics, risk factors and prophylaxis of CIN, only a few authors have published protocols concerning the management of patients undergoing contrastographic examinations. A review of the study group from the Mayo Clinic has prepared a memorandum addressed to the Interventional Radiologists (30). The protocol includes first of all a division of the patients in to three groups based on age, risk factors and eGFR, in order to choose the right prophylactic therapy. Among the recommendations sCr measure concentration after administration of NAC and the cancellation or delay of the procedures if NAC is not administered are prohibited. Post-procedural control is carried out after 2-3 days. Nicola and collaborators recently offered a new protocol which, although similar to the Mayo Clinic, does not provide follow-up controls for very low-risk patients (31).
Also, in this case, attention to the potentially dangerous drugs and their suspension (Table 3) is stressed.

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>Risk</th>
<th>Recommendations</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>Very low risk</td>
<td>Hold metformin for 48 h pre/post procedure; Encourage oral fluids until 2 h preprocedure</td>
<td>No follow-up required</td>
</tr>
<tr>
<td>30-59</td>
<td>Moderate risk</td>
<td>Consider a noncontrast study; Discontinue nephrotoxic meds, hold 24-48 h, metformin 48 h; IV isotonic NaCl (0.9%); 1.0-1.5 mL/kg/h, 3-12 h pre and 6-24 h post; Limit contrast volume &lt;30 mL, diagnostic intervention; Consider LOCM or IOCM; Consider NAC 1200 mg orally twice daily pre and postprocedure</td>
<td>SCr in 48-72 h</td>
</tr>
<tr>
<td>&lt;30</td>
<td>High risk</td>
<td>Consider noncontrast CT; Hospital admission; Consider nephrology consult; Consider hemofiltration pre and postprocedure; Strategies as indicated for eGFR 30-59</td>
<td>SCr before discharge and/or 24-72 h</td>
</tr>
</tbody>
</table>

Table 3 - Nicola et al (31) paradigm for CIN management - CT: computed tomography; eGFR: estimated Glomerular Filtration Rate; IOCM: iso-osmolar contrast media; LOCM: low-osmolar contrast media.

6. Conclusions

CIN is a condition that occurs rarely if patient candidates for contrastographic procedure are previously prepared for this eventuality. A few precautions and proper use of the laboratory indices (sCr, eGFR) are essential tools to control renal function, such as indirect index of CM metabolism. The occurrence of CIN, although symptomatic in a few cases, must be quickly detected and treated, involving other specialists. The physician (radiologist, vascular surgeon, interventional cardiologist, etc.) should distinguish between patients based on their risk of CIN in order to propose the best possible prophylaxis to prevent a reversible, but potentially fatal event.

References