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Review

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.

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 1.73m^2 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,

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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 Iothalamate) (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).

Patient-related risk factors		Procedure-related risk factors
Modifiable	*Unmodifiable*	
Established risk factors		
Dehydration	Preexisting kidney disease	High-osmolar CM
Hypoalbuminemia (<35 g/L)	Diabetes with chronic kidney disease	Ionic vs. non-ionic CM
Poor heart function or hemodynamic instability	Age > 75 y	High-viscosity CM
Preprocedure intra-aortic balloon pump Intra-arterial vs. intravenous injection	Anemia or postprocedure drop in hematocrit	High volume of CM
Hypotension		Multiple CM injections within 72 h
Conflicting (doubtful) risk factors		
Advanced heart failure	Female	Low-osmolar CM in high-risk patients
Left ventricular ejection fracture <40%	Multiple myoloma	
Use of ACEI or ARB	Acute myocardial infarction or increased CK-MB	
Concurrent nephrotoxic medication	Cirrhosis	
NSAIDs, aminoglycoside, amphotericin B, high-dose diuretics, antiviral drugs such as acyclovir and foscarnet, cyclosporine A	Need for cardiac surgery after contrast exposure	
	Urgent or emergent procedure	
	Peripheral vascular disease	
	Diabetes with normal renal function	
	Renal transplant	
New risk factors		
	Metabolic syndrome	
	Prediabetic condition	
	Hyperuricemia	

Table 1 - CIN risk factors - *ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CK-MB: creatine phosphokinase MB isoenzyme; CM: contrast media; NSAIDs: nonsteroidal anti-inflammatory drugs - Modified from Chang et al. (11).*

Other studies use sCr to calculate the maximum dose of CM: 5mL x body weight in kilograms / sCr (mg / mL) (16,17). Some suggest a CM preparation at 37°C to lower its viscosity and an injection at the lowest possible dose to obtain good images (11).

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).

Author, year		Ji et al (24), 2015	Mehran et al (18), 2004		Tziakas et al (20), 2011	Bartholomew et al (22), 2004
Patients		805	5571		688	20479
Number of variables		14	Model A° - 8	Model B^ - 8	5	8
Variables and Scores	0	CFK I	-	-	-	-
	1	Age≥75y BMI≥25kg/m^2 Myoglobin<1000 Hypoalbuminemia CFK II IAPB	each 100mL of CM	each 100mL of CM	History of PCI CM >300mL	CM>260 mL PVD Hypertension CHF DM
	2	Myoglobin 1000-2000 CFK III PVD CM>200mL	-	eGFR 40-60	Pre-existing CKD Metformin PVD	Urgent/Emergency procedure IAPB CrCl<60ml/min
	3	Myoglobin>2000 CFK IV History of CKD	Anemia DM	Anemia DM	-	-
	4	-	sCr>1.5mg/dL Age>75	Age>75 eGFR 20-40	-	-
	5	-	Hypotension IABP CHF	Hypotension IABP CHF	-	-
	6	-	-	eGFR<20	-	-
CIN risk >20% if score sum is*		>5	>8		>2	>7
AUC (p<.010)		0.917	0.899		0.705	0.914

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 m^2); 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.% 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 anotherstudy 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/1.73m^2.

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.

GFR (mL/min)	Risk	Recommendations	Follow-up
>60	Very low risk	Hold metformin for 48-h pre/post procedure Encourage oral fluids until 2-h preprocedure	No follow-up required
30-59	Moderate risk	Consider a noncontrast study Discontinue nephrotoxic meds, hold 24-48 h, metformin 48 h IV isotonic (NaCl/NaHCO3) 1.0-1.5 mL/kg/h, 3-12 h pre and 6-24 h post Limit contrast volume <30 mL, diagnostic <100 mL, diagnostic intervention Consider LOCM or IOCM Consider: NAC 1200 mg orally twice daily pre and postprocedure	SCr in 48-72 h
<30	High risk	Consider noncontrast CT Hospital admission Consider nephrology consult Consider hemofiltration pre and postprocedure Strategies as indicated for eGFR30-59	SCr before discharge and/or 24-72 h

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 cardiology, 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

1. Cotton DB. Radiocontrast-induced renal failure. Lancet 1979; 2:1378–9.

2. Tepel M, Aspelin P, Lameire N. Contrast-inducednephropathy: a clinical and evidence-based approach. Circulation, 2006; 113:1799–1806.

3. Solomon R,Werner C, Mann D et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331:1416–20.

4. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39:930–6.

5. : Geraci G, Mulè G, Cacciatore V, et al. Bilateral renal artery stenosis in a hypertensive lupus patient without renal dysfunction: A case report. EuroMediterranean Biomedical Journal 2014; 9: 41-44

6. McCullough PA, Wolyn R, Rocher LL et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103:368–75.

7. Barrett BJ. Contrast nephrotoxicity. J Am Soc Nephrol 1994; 5:125-37.

8. Hardiek KJ, Katholi RE, Robbs RS, Katholi CE. Renal effects of contrast media in diabetic patients undergoing diagnostic or interventional coronary angiography. J Diabetes Complications 2008; 22: 171-177.

9. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? Biomed Res Int. 2013; 2013:123589.

10. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1–S266.

11. Chang CF, Lin CC. Current concepts of contrast-induced nephropathy: a brief review. J Chin Med Assoc 2013; 76: 673-81.

12. Nawaz S, Cleveland T, Gaines PA, Chan P. Clinical risk associated withcontrast angiography in metformin treated patients: a clinical review. Clin Radiol 1998;53: 342-344.

13. Barrett BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of highand low-osmolality iodinated contrast media. Radiology 1993; 188:171-8.

14. Kushner FG, Hand M, Smith Jr SC, King 3rd SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009; 54: 2205-41.

15. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989; 86: 649-52.

16. Liu Y, Tan N, Zhou YL, He PC, Luo JF, Chen JY. The contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy after primary percutaneous coronary intervention. Int Urol Nephrol 2012; 44: 221-9.

17. Laskey WK, Jenkins C, Selzer F, Marroquin OC, Wilensky RL, Glaser R, et al. Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. J Am Coll Cardiol 2007; 50: 584-90.

18. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous intervention. J Am Coll Cardiol 2004; 44: 1393-1399.

19. Abellás-Sequeiros RA, Raposeiras-Roubín S, Abu-Assi E, González-Salvado V et al Mehran contrast nephropathy risk score: Is it still useful 10 years later? J Cardiol 2016; 67: 262-7

20. Tziakas D, Chalikias G, Stakos D, Apostolakis S, Adina T, Kikas P. Development of an easily applicable risk score model for contrast-induced nephropathy prediction after percutaneous coronary intervention: a novel approach tailored to current practice. Int J Cardiol 2013;163:46-55.

21. Tziakas D, Chalikias G, Stakos D, Altun A, Sivri N, et al. Validation of a new risk score to predict contrast-induced nephropathy after percutaneous coronary intervention. Am J Cardiol 2014; 113: 1487-93.

22. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S, Grines CL, O'Neill WW. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol 2004; 93: 1515-9.

23. Ghani AA, Tohamy KY. Risk score for contrast induced nephropathy following percutaneous coronary intervention. Saudi J Kidney Dis Transpl 2009; 20: 240-5.

24. Ji L, Su X, Qin W, Mi X, Liu F, Tang X, Li Z, Yang L. Novel risk score of contrast-induced nephropathy after percutaneous coronary intervention. Nephrology (Carlton) 2015; 20: 544-51.

25. Mueller C, Buerkle G, Buettner HJ et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002; 162: 329-36.

26. Jang JS, Jin HY, Seo JS, Yang TH et al. Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury – a systematic review and meta-analysis –. Circ J 2012; 76: 2255-65.

27. Briguori C, Airoldi F, D'Andrea D et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation 2007; 115: 1211-7.

28. Pattharanitima P, Tasanarong A. Pharmacological strategies to prevent contrast-induced acute kidney injury. Biomed Res Int 2014; 2014: 236930.

29. Owen RJ, Hiremath S, Myers A, et al. Canadian Association of Radiologists consensus guidelines for the prevention of contrast-induced nephropathy: Update 2012. Can Assoc Radiol J 2014; 65: 96–105.

30. Goldfarb S, McCullough PA, McDermott J, Gay SB. Contrast-induced acute kidney injury: specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. Mayo Clin Proc 2009; 84:170-9.

31. Nicola R, Shaqdan KW, Aran K, Mansouri M, Singh A, Abujudeh HH. Contrast-Induced Nephropathy: Identifying the Risks, Choosing the Right Agent, and Reviewing Effective Prevention and Management. Curr Probl Diagn Radiol. 2015; 44: 501-4