

Core Curriculum

Prevention of Contrast Induced Nephropathy: Recommendations for the High Risk Patient Undergoing Cardiovascular Procedures

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Contrast induced nephropathy (CIN) is the third leading cause of hospital acquired renal failure and is associated with significant morbidity and mortality. Chronic kidney disease is the primary predisposing factor for CIN. As estimated glomerular filtration rate <60 ml/1.73 m² represents significant renal dysfunction and defines patients at high risk. Modifiable risk factors for CIN include hydration status, the type and amount of contrast, use of concomitant nephrotoxic agents and recent contrast administration. The cornerstone of CIN prevention, in both the high and low risk patients, is adequate parenteral volume repletion. In the patient at increased risk for CIN it is often appropriate to withhold potentially nephrotoxic medications, and consider the use of n-acetylcysteine. In patients at increased risk for CIN the use of low or iso-osmolar contrast agents should be utilized and strategies employed to minimize contrast volume. In these patients serum creatinine should be obtained forty-eight hours post procedure and it is often appropriate to continue withholding medications such as metformin or non steroidal anti-inflammatories until renal function returns to normal.

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TABLE I. Radiographic Contrast Agents

| Product | Type of contrast agent concentration | Mg (1/ml) | Osmality (mOsm/l) |
|-----------------------|--------------------------------------|-----------|-------------------|
| <i>Monomers</i> | | | |
| Iohexol (Omnipaque) | Nonionic LOCM | 350 | 844 |
| Iopamidol (Isovue) | Nonionic LOCM | 370 | 796 |
| Ioxilan (Oxilan) | Nonionic LOCM | 350 | 695 |
| Iopromide (Ultravist) | Nonionic LOCM | 370 | 774 |
| Ioversol (Optiray) | Nonionic LOCM | 350 | 792 |
| <i>Dimers</i> | | | |
| Iodixanol (Visipaque) | Nonionic IOCM | 320 | 290 |
| Ioxaglate (Hexabrix) | Ionic LOCM | 320 | 600 |

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TABLE II. Equations to Estimate CrCl and GFR

I. Cockcroft–Gault (C&G) estimates CrCl (ml/min)

$$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{SCr (mg/dl)}}$$

II. Modification of diet in renal disease (MDRD) estimates GFR (ml/min/1.73 m²)^a

$$\frac{170 \times (\text{SCr} \times 0.011)^{-0.999} \times (\text{age})^{-0.176} \times (\text{SUR} \times 2.801)^{-0.170}}{(\text{SA1b} \times 0.1)^{0.318} \times 1.180 \text{ (if black)} \times 0.762 \text{ (if female)}}$$

SCr, serum creatinine; SUR, serum urea; SA1b, serum albumin. The calculator for MDRD is located on the internet at: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm OR http://www.nkdep.nih.gov/professionals/gfr_calculators/mdrd_con.htm

^aThis does not require patient weight.

INTRODUCTION

The invasive/interventional cardiologist uses radiographic contrast media (RCM) on a daily basis and must strive to minimize the risks associated with these agents. One such risk, contrast induced nephropathy (CIN), is defined as a worsening of renal function after RCM administration. The medical literature varies in the definition of CIN, typically using a change in serum creatinine (SCr) over baseline by 48 hr, such as $\geq 25\%$ above baseline or an absolute increase of >0.25 or 0.5 mg/dl [1–3]. Albeit an infrequent event in unselected population-based studies, CIN is the third leading cause of all cases of hospital-acquired renal failure [4].

In recognition of the need for a document on the prevention of CIN, the Society for Cardiovascular Angiography and Interventions (SCAI) proposes the following recommendations based on the available evidence in the literature, and where inconclusive, supplemented by consensus.

ESTIMATION OF CIN RISK AND PATIENT OUTCOMES

Adverse reactions have been the major disadvantage of RCM since their introduction for urinary tract visualization in 1923. High-osmolar ($>1,600$ mOsm/l) ionic RCM (HOCM) were the first agents developed and are produced using the meglumine and sodium salts of diatrizoic acid. Low-osmolar (<850 mOsm/l) RCM (LOCM), both ionic and nonionic, have increasingly supplanted HOCM in clinical practice as they have less systemic adverse effects. These agents (Table I) are predominantly monomeric, non-ionic agents with the exception of the two dimers: ioxaglate (ionic) and iodixanol (non-ionic).

Chronic kidney disease (CKD) is the primary predisposing factor for CIN [5]. Definitions of CKD in the medical literature have varied and have relied on the SCr rather than creatinine clearance (CrCl) or glomerular filtration rate (GFR). Equations for estimating CrCl and GFR (Table II) are based upon age, body weight, and sex, and with Modification of Diet in Renal Disease (MDRD), race, and serum albumin. MDRD is preferred in the obese or elderly patient [6,7]. Both formulae are more accurate measures of intrinsic renal function than SCr alone [6,7].

Though limitations exist with each method/formulae [8], the MDRD is recommended to estimate GFR in the adult patient with cardiovascular disease [9]. It should be noted that there are two versions of the MDRD equation; the abbreviated version requires fewer measured parameters while providing essentially the same results. These are available online: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm or http://www.nkdep.nih.gov/professionals/gfr_calculators/mdrd_con.htm.

In addition to CKD, there are patient-related risk factors for CIN [10–13]. Table III summarizes the

TABLE III. Pre-procedural Clinical Risk Factors for CIN

| Modifiable risk factors | Non-modifiable risk factors |
|---------------------------------|-----------------------------------|
| Contrast volume | Diabetes |
| Hydration status | Chronic kidney disease |
| Concomitant nephrotoxic agents | Shock/hypotension |
| Recent contrast administrations | Advanced age (>75 years) |
| | Advanced congestive heart failure |

CIN, contrast-induced nephropathy.

most commonly encountered modifiable and non-modifiable pre-procedural clinical features associated with CIN.

The risk of CIN is inversely related to the calculated estimated GFR (eGFR) [13]. An eGFR of <60 ml/min/1.73 m² represents significant renal dysfunction [14] and is used to define the patient at high risk for developing CIN.

Several predictive algorithms have been proposed to estimate the risk for CIN. These algorithms generally include intraprocedural factors limiting their use prior to the procedure with none prospectively validated. Mehran developed a risk score for predicting CIN [10] that includes congestive heart failure, hypotension, age >75 years, anemia, diabetes, RCM volume, and CKD defined as a SCr >1.5 mg/dl or an eGFR of <60/ml/min/1.7 m². Of note, the risk of CIN increases in a graded fashion as the eGFR decreases from <60/ml/min/1.7 m² to <20/ml/min/1.7 m².

The development of CIN is strongly associated with significant morbidity and mortality. Among hospital survivors who undergo percutaneous coronary intervention (PCI), patients who develop CIN are at an increased risk of death or myocardial infarction (MI) at 6 months, 1 year, and 5 years [15,16]. Rihal reported an in-hospital mortality of 22% in the 254 patients who developed CIN following PCI, from a patient population of 7,586 [13]. Acute hemodialysis was uncommon except in patients with severe CKD, especially when diabetes was present. McCullough studied 1,826 patients undergoing PCI with an in-hospital mortality of 1.1% in patients without CIN, 7.1% in patients with CIN without dialysis, and 35.7% in dialyzed patients with CIN [15].

PRE-PROCEDURAL MANAGEMENT FOR THE HIGH RISK PATIENT

Volume Repletion

Multiple trials have addressed type, amount, duration, and route of volume repletion to prevent CIN [17–20]. Small numbers, different patient populations and endpoints, and various repletion regimens have hindered comparison of these studies. Mueller randomized 1,620 patients undergoing PCI to isotonic (normal) saline or

half normal saline with the incidence of CIN significantly decreased in the isotonic saline group compared with half-normal saline (0.7% vs. 2.0%) [21]. Importantly, all studies agree parenteral volume repletion is the cornerstone of CIN prevention [22].

The critical aspect is to ensure optimal volume repletion prior to the procedure. With many protocols published but no one specific regimen identified, it is strongly recommended to parenterally administer a total of at least 1 L of isotonic saline beginning at least 3 hrs before and continuing at least 6–8 hrs after the procedure. Initial infusion rates of 100–150 ml/hr are recommended with adjustment post procedure as clinically indicated. Appropriate caution should be applied in the patient with known reduced left ventricular function or congestive heart failure. To accomplish this regimen, outpatients should be scheduled for early arrival or later procedure times; prior-day admission may be required in selected patients.

Sodium Bicarbonate. The use of isotonic sodium bicarbonate has been demonstrated in one study to be marginally superior to isotonic sodium chloride (saline) in preventing CIN in the high risk patient [23]. This protocol used an infusion of 3 ml/kg/hr for 1 hr before and 1 ml/kg/hr for 6 hrs after the procedure. Although additional studies are needed, these data suggest that a modified regimen with sodium bicarbonate may be effective in the high risk patient.

Patient Medications

Pre-procedural management of patients at risk for CIN requires a review of the patient's medications and withholding, as clinically appropriate, potentially nephrotoxic drugs, including aminoglycoside antibiotics, anti-rejection medications, and nonsteroidal anti-inflammatory drugs (NSAID). Although optimizing volume status is essential, the decision to interrupt diuretic therapy must be individualized [13,17,21]. Angiotensin converting enzyme inhibitor therapy may be continued but neither initiating nor changing dose should be considered until the patient is safely past the risk period for CIN following RCM. Although not a risk factor for developing CIN, metformin should be withheld after the procedure until it is clear that renal function has not significantly deteriorated [24].

Pharmacotherapy

Table IV summarizes the multiple pharmacologic approaches to mitigate the risk for CIN [25]. Many agents studied have not shown a consistent benefit in reducing the incidence of CIN when compared to volume repletion alone. These include mannitol [17], post-procedural diuretics [17], dopamine [26], fenoldopam [27], atrial natriuretic peptide [28], non-selective

TABLE IV. Approach to Prevention of CIN Based on Possible Etiologic Mechanisms

| Hemodynamic-vascular | Cytotoxic-free radical | Other |
|--|---|---------|
| <i>Possibly beneficial</i> | | |
| Aminophylline/theophylline Prostaglandin E1 | <i>N</i> -Acetylcysteine (NAC) Sodium bicarbonate Ascorbic acid | Statins |
| <i>Not Proven Beneficial</i> | | |
| Angiotensin II Fenoldopam Dopamine Calcium-channel blocker Endothelin antagonists Adenosine | | |

CIN, contrast-induced nephropathy.

endothelin receptor antagonists [29], and calcium channel blockers [30]. Potential benefits may occur with prostaglandin E1 [31], aminophylline or theophylline [32], statins [33], and ascorbic acid [34] but more data are needed before any of these agents can be systematically recommended.

Despite multiple single studies, as well as several meta-analyses, the true benefit of *N*-acetylcysteine (NAC) is still unclear [35–37]. However, NAC remains the most frequently prescribed medication in this setting, as a likely consequence of its low cost and lack of serious side effects. If chosen, 600 mg of NAC should be administered orally q 12 hrs × 4 doses by mixing it with soda or orange juice and begun prior to RCM.

INTRA-PROCEDURAL MANAGEMENT FOR THE HIGH RISK PATIENT

Contrast Volume

Total case RCM volume is a risk factor for CIN [10,13]. Intuitively, the less RCM administered, the lower the risk for CIN. However, there are no studies that prospectively evaluate this hypothesis. Retrospective analyses have suggested that a total dose of <30 ml for diagnostic studies and <100 ml for interventional procedures lessen the risk for CIN [10]. In a study by Freeman, RCM doses above 5 cc × body weight (kg)/SCr were associated with a need for dialysis while unadjusted RCM dose was not a univariate predictor of contrast induced dialysis [38].

The complexity and unpredictability of PCI precludes a strict recommendation of the RCM dose for a particular procedure. Measures recommended to decrease RCM volume in the high risk patient include small catheter size, biplane or rotational coronary angiography, and avoidance of left ventriculography. Performing diagnostic and interventional procedures at separate sessions, often referred to as *staging*, is appro-

TABLE V. Summary of Randomized Clinical Trials Concerning Type of RCM and Relative Risk of CIN in High Risk Patients Undergoing Angiographic Procedures

| Trial (Reference) | Outcome RR (95% CI) |
|-------------------|---------------------|
| LOCM vs HOCM | |
| Taliercio [39] | 0.44 (0.19–1.06) |
| Schwab [40] | 0.94 (0.40–2.20) |
| Rudnick [11] | 0.58 (0.42–0.78) |
| Barrett [41] | 1.14 (0.39–3.34) |
| IOCM vs LOCM | |
| Aspelin [42] | 0.09 (0.02–0.41) |
| Chalmers [43] | 0.33 (0.06–1.79) |
| Meta-analyses | |
| Barrett [44] | 0.50 (0.36–0.68) |
| McCullough [45] | 0.31 (0.15–0.65) |

RCM, radiographic contrast media; RR, relative risk; CIN, contrast-induced nephropathy; CI, confidence interval; IOCM, iso osmolar contrast media; LOCM, low osmolar contrast media; HOCM, high osmolar contrast media.

appropriate if the clinical situation permits. However, there are limited data regarding the timing for a repeat procedure with RCM. With creatinine elevation post RCM occurring by 48–72 hrs, it is recommended to consider avoiding subsequent RCM during this period.

Radiographic Contrast Media

Table V summarizes the randomized clinical trials (RCTs) regarding the type of RCM and the incidence of CIN in the high risk patient.

Overall, there is evidence that LOCM lessens the risk for CIN in the high risk patient compared with HOCM [44]. It is unclear whether significant differences in nephrotoxicity exist among individual LOCM [46]. One RCT has demonstrated a lessened risk for development of CIN in the high risk patient with iso-osmolar contrast media compared to a single LOCM [42]; additional RCTs are ongoing.

Gadolinium chelates are used extensively in magnetic resonance imaging, and reports of CIN are rare. These agents have been proposed as an alternative to iodinated agents in the high risk patient for CIN, but no benefit has been reported to date [47].

POST-PROCEDURAL MANAGEMENT FOR THE HIGH RISK PATIENT

Volume Repletion

Continuation of pre-procedure parenteral volume repletion is the mainstay of post-procedural management in the high risk patient for CIN. To ensure adequate hydration, urine output should be monitored. Though a urine output of 150 ml/hr is preferred [20], individual assessment is required. The risk/benefit ratio for bladder catheterization to monitor urine output should be considered.

TABLE VI. Recommendations for Prevention of CIN

1. Identify Risk
 - a. Low risk – eGFR > 60 ml/1.73 m²
 - i. Optimize hydration status.
 - b. High risk – eGFR < 60 ml/1.73 m²
 - i. Schedule outpatient for early arrival or delay procedure time to allow time to accomplish the hydration.
 - ii. Consider the following recommendations (No. 2–No. 5).
2. Manage medications
 - a. Withhold, if clinically appropriate, potentially nephrotoxic drugs including aminoglycoside antibiotics, anti-rejection medications and nonsteroidal anti-inflammatory drugs (NSAID).
 - b. Administer *N*-acetylcysteine (equivocal data, see text)
 - i. 600 mg administered orally q 12 hrs × 4 doses beginning prior to contrast.
3. Manage Intravascular Volume (Avoid Dehydration)
 - a. Administer a total of at least 1 L of isotonic (normal) saline beginning at least 3 hrs before and continuing at least 6–8 hrs after the procedure.
 - i. Initial infusion rate 100–150 ml/hr adjusted post procedure as clinically indicated.
 - b. Sodium bicarbonate^a (limited data, see text)
 - i. 154 mEq/l @ 3 ml/kg/hr starting 1 hr before contrast.
 - ii. 154 mEq/L @ 1 ml/kg/hr for 6 hrs following contrast.
4. Radiographic contrast media
 - a. Minimize volume.
 - b. Low- or iso-osmolar contrast agents (on going data, see text).
5. Post-procedure: discharge/follow-up
 - a. Obtain follow-up SCr 48 hrs post procedure.
 - b. Consider holding appropriate medications until renal function returns to normal, i.e. metformin, NSAID.

CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; SCr, serum creatinine. ^a154 mEq/L is 3 A NaHCO₃ in 1 L of either D5W or sterile water.

Hemofiltration

Hemodialysis has been shown to remove RCM but not to prevent CIN [48]. Hemofiltration allows increased hemodynamic stability compared with hemodialysis while permitting 10–15 times the usual hydration without adding intravascular volume. Though promising in small studies, hemofiltration is invasive and logistically complex [49,50]. It will need to be established in larger trials before it can be widely recommended.

Follow-Up

Management following RCM administration depends on the risk for CIN, with little follow-up required for the low risk patient. In the high risk patient, SCr should be obtained at 48–72 hrs following RCM as 24 hr values will miss a significant minority of these events. It should also be noted that the peak decrement in renal function may not appear until 1 week. Restarting medications such as NSAID's and metformin is dependent upon the return to baseline renal function [25]. Should renal dysfunction occur, other causes

should be considered, e.g. cholesterol embolization, which is commonly associated with skin lesions [51].

CONCLUSIONS AND RECOMMENDATIONS (TABLE VI)

The risk of CIN varies from 2–30% in unselected patients undergoing cardiovascular angiographic procedures. It is associated with a significant increase in patient morbidity and mortality. Recognition of the high risk patient coupled with appropriate peri-procedural management can reduce the incidence of CIN. The routine use of eGFR is strongly recommended as a method to identify the patient at risk for CIN. The available evidence to date supports vigorous parenteral volume repletion, limiting contrast volume, and the use of low- or iso-osmolar contrast media to decrease the incidence of CIN in the high risk patient.

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