

Contrast-induced Kidney Injury: Focus on Modifiable Risk Factors and Prophylactic Strategies

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ABSTRACT

Contrast-induced nephropathy, also known as contrast-induced acute kidney injury, is associated with rapid and often irreversible decline in kidney function following the administration of iodinated contrast agents. Contrast-induced nephropathy is the third leading cause of acute kidney injury in hospitalized patients, and substantially increases mortality, morbidity, and length of hospitalization. Contrast-induced nephropathy follows a predictable time of onset and is potentially preventable. It has been the subject of numerous studies addressing characteristics of the populations at risk and prophylactic strategies. This evidence-based review summarizes recent literature and provides a nephrologists' perspective on contrast-induced nephropathy, focusing on: the pathophysiology of contrast-induced nephropathy; identification of populations at risk; correlation between contrast-induced nephropathy and the type of contrast agent used; and finally, measures to prevent contrast-induced nephropathy, including intravenous fluids, sodium bicarbonate, N-acetylcysteine, and hemofiltration/hemodialysis.

Introduction

Contrast-induced nephropathy (CIN) is a common and serious complication of radiocontrast administration used in imaging studies, and is the third leading cause of acute kidney injury (AKI) in hospitalized patients.¹ No consensus exists on the definition of CIN, however, in recent literature, an increase in serum creatinine (SCr) of ≥ 0.5 mg/dL, or more than 25% above baseline has been used to define CIN. Reported incidence of CIN varies based on the definitions used, populations studied, and specific clinical settings. In a registry of more than 7500 patients who underwent interventional cardiac procedures, 3.3% developed CIN.² Similar incidence of CIN has been reported in other registries of the general population undergoing coronary angiography.³ Incidence of CIN is significantly increased in patients with chronic kidney disease (CKD) and diabetes, reaching nearly 50% in select subgroups.^{2,4} Acute kidney injury following contrast medium administration carries significant mortality risk; multiple studies have demonstrated a 2-fold to 5-fold increase in risk for both short-term and long-term mortality in patients with CIN.^{4,5} In addition, development of CIN is associated with a higher risk of myocardial infarction, neurologic complications, need for revascularization of target vessels, and has been shown to result in an increased length of hospital stay.⁶

Risk Factors

Baseline kidney function strongly determines the risk of CIN,⁷ and the degree of kidney impairment at baseline correlates with a proportionate risk for CIN. Among patients in the Minnesota Registry of Interventional Cardiac

Procedures, CIN was diagnosed in 22% of patients with SCr > 2 mg/dL and in 30% of patients with SCr > 3 mg/dL.² Diabetes, increased age, higher dose of contrast agent used, route of contrast administration (intra-arterial vs intravenous), congestive heart failure (CHF), hypertension, periprocedural shock, baseline anemia, postprocedural drop in hematocrit, use of nephrotoxins, and nonsteroidal anti-inflammatory medications, volume depletion, increased CK-MB, and need for cardiac surgery after contrast exposure, have been associated with increased risk of CIN.^{2,5} Mehran et al devised an algorithm for risk prediction of CIN and the need for dialysis in a general population of patients who underwent coronary angiography, and subsequently validated the prediction score in a separate cohort of patients, 26% of whom had CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min).⁸ A cumulative score based on the presence of hypotension, use of an intra-arterial balloon pump, evidence of CHF, age > 75 , anemia, diabetes, large volume of contrast medium used, and the degree of kidney impairment, predicts a cumulative risk of CIN from 7.5% to 57%, and the need for dialysis from 0.04% to 12.6%. Naturally, correction of hypotension and anemia, optimization of heart failure, and minimizing contrast volume/dose (avoid repeated contrast studies until the kidneys recover from a prior insult, and use minimal dose of contrast needed to obtain the necessary information), may reduce the cumulative risk of CIN.

Pathophysiology

The pathophysiology of CIN in humans is not clearly established, and is likely multifactorial. Several mechanisms

have been proposed to explain the pathogenesis of CIN. Intra-arterial infusion of contrast medium results in initial vasodilation, followed by vasoconstriction, accompanied by shunting of blood flow from the medulla to the cortex, with a net result of a 20% increase in blood flow to the cortex and a 40% decrease in blood flow to the medulla; the medullary ischemia (60% decrease in oxygen delivery) that ensues is thought to contribute to tubular injury.⁹ Direct cytotoxicity to the tubular epithelial cells has been demonstrated, as evident by vacuolization and tubular epithelial cell death; in addition, increased viscosity of tubular fluid has been proposed to cause stasis, potentially contributing to kidney dysfunction.⁹ Finally, production of reactive oxygen species and subsequent tubular damage have been demonstrated in a number of animal studies.⁹ Mediators of vasoconstriction, including adenosine, endothelin, and altered nitric oxide have been implicated in the pathogenesis of CIN, however, clinical trials aimed at these targets for therapeutic purposes have had limited success in preventing kidney injury.⁹

Preventive Strategies

Contrast Medium

Early studies have demonstrated increased risk of CIN with high osmolality contrast agents. Recently, several studies examined the risk of CIN in patients with underlying CKD using isosmolar contrast medium (IOCM; 290 mosmol/kg H₂O) or low osmolality contrast medium (LOCM; 300–900 mosmol/kg H₂O)¹⁰; odds ratio (OR) for the development of CIN was 0.09 for IOCM (iodixanol) compared to LOCM (iohexol). Similar results were demonstrated in the Feasibility Study of Radiofrequency Heating of Cardiac Infarction Scar to Treat Heart Failure (RECOVER) trial¹¹; 300 patients with CKD received either IOCM (iodixanol) or LOCM (ioxaglate); OR for the development of CIN was 0.415, favoring the use of IOCM. Beneficial effects extended to subgroup analysis in patients with CKD, diabetes, those receiving higher dose of contrast medium, and patients with a mildly depressed ejection fraction; however, no mortality benefit was observed.¹¹ Similarly, in patients with moderate CKD (eGFR <60 mL/min) receiving IV contrast for non-emergent CT scanning, IOCM (iodixanol) decreased the risk of mild AKI (SCr >0.5, but not >1 mg/dL); however, in a subgroup analysis of patients receiving prophylactic therapy (intravenous fluids, sodium bicarbonate, and/or N-acetylcysteine [NAC]), the protective effects of IOCM compared to LOCM were no longer observed.¹² In agreement with this subgroup analysis,¹² the CARE trial,¹³ a multicenter study of 414 patients with moderate to severe CKD (eGFR 20–59 mL/min) undergoing angiography and treated with isotonic bicarbonate infusion, IOCM (iodixanol) offered no benefit over LOCM (iopamidol) in preventing CIN. Additionally, in the VALOR trial,¹⁴ use of IOCM (iodixanol) offered no advantage over LOCM (ioversol)

in CKD patients (SCr ≥1.7 mg/dL in men and ≥1.5 mg/dL in women) undergoing coronary angiography and treated with NAC and intravenous fluids. Although, patients with CKD and diabetes mellitus (DM) who received LOCM had relatively higher SCr, the risk of CIN (defined as an increase in SCr ≥0.5 mg/dL) was not significantly different between the 2 groups.¹⁴ Finally, a recent small multicenter trial (ACTIVE trial)¹⁵ comparing IOCM (iodixanol-320) and LOCM (ioimeprol-400) in patients with CKD demonstrated favorable results for LOCM (ioimeprol) compared to IOCM (iodixanol); LOCM appeared to have a protective effect compared to IOCM (0% vs 6.9%).¹⁵ A meta-analysis of 2727 patients enrolled in 16 separate trials showed decreased risk of CIN associated with use of IOCM compared to LOCM.¹⁶ Given the above findings, the CIN Consensus Working Panel concluded that “Current evidence suggests that for intra-arterial administration in high-risk patients with CKD, particularly those with diabetes mellitus, nonionic, iso-osmolar contrast is associated with the lowest risk of CIN.”¹⁷

The dose of contrast agent administered is important: based on a registry of 9242 patients undergoing cardiac catheterization and percutaneous coronary intervention, exceeding the weight-adjusted and creatinine-adjusted maximum radiographic contrast dose (calculated as 5 × body weight in kg/SCr) was associated with increased risk of CIN and a need for renal-replacement therapy (OR: 6.2, 95% confidence interval [CI]: 3.0–12.8 for CIN requiring dialysis).¹⁸ Multivariate analyses have established correlation between higher doses of contrast administered (usually >100 mL or >150 mL) and risk for CIN.^{2,4} Consistently, the CIN Consensus Working Panel¹⁷ concluded that “higher contrast volumes (>100 mL) are associated with higher rates of CIN in patients at risk.”

Administration of Fluids

Several studies identified volume depletion as a risk factor for the development of CIN; as a result, fluid administration is frequently recommended. The optimal method and composition of the fluid administered remains to be established; however, isotonic saline is favored over hypotonic solutions. Administration of intravenous isotonic saline carried a lower risk of CIN than unrestricted oral intake in the general population undergoing elective coronary angiography¹⁹; and isotonic intravenous fluid is now preferred over hypotonic solution. In a study of 1383 patients (21% with CKD) undergoing elective or emergent coronary interventions,²⁰ administration of isotonic saline (NS) at 1 mL/kg/hr for 24 hours in the periprocedure period was associated with 0.7% incidence of CIN compared with 2.0% incidence of CIN when 0.45 NS in 5% glucose was used instead.

Bicarbonate

Alkalinization of tubular fluid is thought to diminish tubular toxicity and decrease free radical generation, and has been studied as prophylaxis for CIN. An initial study of 137 patients with CKD (SCr ≥ 1.1 mg/dL) scheduled for contrast administration (coronary angiography, computed tomography, or radiographic procedures) and randomized to receive 3 mL/kg/h of either 5% dextrose with 154 mEq/L sodium chloride (NaCl) or 5% dextrose with 154 mEq/L bicarbonate for 1 hour before contrast administration, followed by an infusion at 1 mL/kg/h for 6 hours after contrast administration,²¹ the incidence of CIN was 1% in patients receiving bicarbonate, compared with 8% in patients receiving saline. Given the highly significant lower risk for CIN in the group assigned to receive bicarbonate, the study was terminated prior to projected completion. Similarly, a single-center trial of 264 patients with CKD (SCr ≥ 1.2 mg/dL), infusion of isotonic bicarbonate at 1 mL/kg/h for 6 hours prior to and 6 hours after contrast medium exposure, was associated with lower incidence of CIN compared with the saline-infused group (4.5% and 13.5%, respectively).²² However, several recent studies failed to demonstrate similar protective effects of sodium bicarbonate: in a single-center study of patients with CKD (eGFR < 60 mL/min) and additional risk factors (at least 1 of the following: hypertension, CHF, DM, or age > 75 years) undergoing non-emergent coronary angiography, sodium bicarbonate (154 mEq/L in 5% dextrose), or isotonic saline infused at 3 mL/kg/h for 1 hour prior to contrast administration and 1 mL/kg/h for 6 hours afterwards, resulted in similar risk of CIN in all treatment groups.²³ Another single-center trial of 502 CKD patients (eGFR < 60 mL/min) scheduled for non-emergent coronary angiography comparing isotonic saline (1 mL/kg/h, started 12 hours before and extended 12 hours after the procedure) against isotonic sodium bicarbonate in dextrose (3 mL/kg/h for 1 hour before, followed by 1 mL/kg/h for 6 hours after contrast administration) given in addition to NAC failed to show superiority of either treatment modality.²⁴ Additionally, the REINFORCE trial,²⁵ a single-center study of 145 patients with CKD (SCr > 1.2 mg/dL) scheduled for elective coronary angiography, treatment with sodium chloride, or sodium bicarbonate (both at 154 mEq/L in 5% dextrose), given at 2 mL/kg/h for 1 hour before contrast administration, followed by 1 mL/kg/h for 6 hours postprocedure, failed to show any difference between the groups. Interestingly, a retrospective review of 7977 patients in a single-center registry, sodium bicarbonate administration had a deleterious effect when compared to no treatment.²⁶

N-acetylcysteine

N-acetylcysteine, a free radical scavenger with reported vasodilatory effects, has been studied in multiple trials to

prevent CIN. An initial report described a single-center experience in 83 patients with CKD (SCr > 1.2 mg/dL) undergoing computed tomography with LOCM; administration of oral NAC at 600 mg twice daily on the day before and the day of procedure, in addition to an infusion of hypotonic saline, reduced the incidence of CIN 10-fold.²⁷ Similarly, a 3-fold reduction in the incidence of CIN was reported in CKD patients undergoing elective coronary angiography following the administration of oral NAC (600 mg) in addition to intravenous isotonic saline.²⁸ However, the benefits of NAC were not consistently observed in other studies. In several single-center trials, administration of NAC orally or intravenously, as an adjunct to saline hydration, provided no beneficial effects.^{22,29,30} A number of meta-analyses published recently attempted to resolve these conflicting results^{31,32}; overall, NAC appears to be beneficial, with an OR from pooled analyses of 0.53 to 0.57. Earlier trials using hypotonic saline infusions and higher doses of contrast medium tended to enhance the benefits of NAC administration. More recent studies suggest that higher doses of NAC may provide a significant protection against CIN: treatment with 1200 mg NAC given orally twice daily on the day before and the day of contrast exposure was associated with lower risk of CIN, compared with 600 mg NAC (3.5% vs 11%).³³ Similarly, a 2.6-fold lower incidence of CIN was shown in patients with ST-elevation acute myocardial infarction who were treated with isotonic saline and 1200 mg IV bolus of NAC followed by 1200 mg oral NAC after emergent coronary intervention compared with patients receiving 600 mg IV bolus of NAC before and 600 mg oral NAC after procedure.³⁴ Of note, this was the only trial to demonstrate a survival benefit of NAC in this high-risk population.

Combination of Prophylactic Measures

Based on results of the REMEDIAL study,³⁵ a 2-center trial of patients with moderate to severe CKD (CrCl < 40 mL/min/1.73 m²), administration of isotonic bicarbonate with NAC (1200 mg) was more protective than NAC and saline. Similarly, in 111 patients with acute coronary syndrome undergoing emergent coronary intervention (RENO trial³⁶; mean SCr at presentation 1.0 mg/dL), intravenous NAC (2400 mg) and sodium bicarbonate given 1 hour prior to contrast administration were more effective in preventing CIN than isotonic saline and oral NAC given postprocedure. However; in a largely negative retrospective analysis of the general population of patients undergoing coronary angiography,²⁶ use of sodium bicarbonate alone was associated with an increased risk of contrast nephropathy compared with no treatment; while NAC alone or in combination with sodium bicarbonate was not associated with any significant difference in the incidence of contrast nephropathy.²⁶

Hemofiltration and Hemodialysis

In a single-center trial of patients with advanced CKD (Scr >2 mg/dL), hemofiltration started 4 hours before contrast administration (for coronary intervention) and continued for 24 hours after the procedure, compared with isotonic saline administration, prevented the deterioration of renal function after contrast administration, decreased the need for renal replacement therapy, and improved in-hospital and long-term outcomes.³⁷ Similarly, in patients nearing end-stage renal disease (Scr >3.5 mg/dL), a single 4-hour hemodialysis session (initiated immediately after contrast exposure) shortened the length of stay and reduced the need for renal replacement therapy at hospital discharge.³⁸

Preventive Strategies Without Benefit or with Deleterious Effects

Dopamine, fenoldopam (a selective dopaminergic agent), simvastatin, theophylline, iloprost, furosemide, or mannitol do not offer significant protection against CIN,³⁹ and their use is not supported by current evidence.³⁹ Forced diuresis with furosemide or mannitol was associated with an increased risk of CIN in patients with CKD (CrCl <60 mL/min/1.73²) undergoing elective coronary angiography.^{39,40}

Final Remarks

The risk of CIN varies depending on comorbidities, procedures, and clinical settings. Hence, the risk-to-benefit analysis of prophylactic measures applied to individual patients needs to be individualized. Since the majority of published data are derived from coronary or peripheral angiography patients, applicability for computed tomography and other radiographic studies needs to be established. Finally, despite the significant mortality burden of CIN, few trials have demonstrated the mortality benefit of successful renoprotective measures.

Recommendations

1. Consider prophylactic measures in patients at risk for the development of CIN (those with CKD, DM, increased age, and hemodynamic instability).
2. In high-risk patients, minimize the amount of contrast medium administered and use isosmolar agents.
3. Unless contraindicated, consider using NAC on the day before and day of contrast exposure.
4. In an emergency setting, where preparation of the patient with IV hydration is not feasible, consider administration of isotonic sodium bicarbonate with high dose NAC (2400 mg) 1 hour before contrast.
5. Monitor renal function at 24 to 72 hours after contrast administration.

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