Trials and tribulations of diagnosing and preventing contrast-induced acute kidney injury

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Feature Editor’s Introduction—One of the most frustrating and potentially devastating complications after open surgery is acute kidney injury. Although the intraoperative mechanisms that incite it have not been well worked out, clearly, postoperative imaging when accompanied by contrast agents has an association if not a causative role in its development. The well-recognized complications of renal failure, whether requiring hemodialysis or not, with its order of magnitude increase in mortality mandate our understanding of its etiologies to minimize the risk of its development. But even the development of postoperative Kidney Disease Improving Global Outcomes stages 1 and 2 injury convey significant morbidity and mortality, with or without early resolution, extending at least to 1 year postdischarge. Taken as a whole, those experiencing postoperative acute kidney injury dramatically increase the cost of medical care. We all face the recurrent decision in our critically ill patients who require imaging as to the risks and benefits of contrast to enhance the information obtained from those images. In point of fact, imaging without contrast often proves disappointing unhelpful. In the article by Waheed and Choi in the current issue of the Journal, the concise explanation of the etiology and clear description with the associated evidence for current preventive strategies of this frequently unavoidable exposure to contrast-induced nephrotoxicity is a “must read” for all of us who care for these patients postoperatively. The style and content so attractive in this article should be a paradigm for all of us who hope to convey a message across specialty boundaries.

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The majority of patients undergoing cardiovascular surgery require imaging with contrast-enhanced computed tomography or angiography and are inevitably exposed to iodinated contrast in the process. The development of acute kidney injury (AKI) as a result of iodinated contrast exposure is a multifactorial process. AKI is likely to be multifactorial in these patients who are labeled as having contrast-induced AKI (CI-AKI), it has been difficult to ascertain the exact incidence of CI-AKI. Underlying factors such as the presence of preexisting kidney disease and the route, amount, and osmolality of iodinated contrast used may have an effect on the incidence of CI-AKI; therefore, the incidence rates quoted in the literature are variable.

A systematic review reported that CI-AKI risk has been overestimated because any AKI temporally linked to contrast exposure has been labeled CI-AKI without establishing causality. Certain modifiable risk factors can increase CI-AKI rates.

CENTRAL MESSAGE

CI-AKI risk has been overestimated because any AKI temporally linked to contrast exposure has been labeled CI-AKI without establishing causality. Certain modifiable risk factors can increase CI-AKI rates.

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was a temporal relation. Recent studies have shown that actual true demonstrable incidence of AKI caused by contrast administration is lower and have even questioned the existence of CI-AKI. There is no doubt that the risk of CI-AKI has been overestimated over the years, but there is still a subset of patients who might experience kidney damage from administration of iodinated contrast. Given that development of AKI is an independent predictor of postoperative mortality, it is imperative for clinicians to recognize patients who are at increased risk of developing CI-AKI and minimize the modifiable risk factors. In this review, we will discuss the diagnosis of CI-AKI and how to identify high-risk patients and practices that can decrease the risk of developing CI-AKI.

MECHANISM OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

Iodinated contrast causes renal vasoconstriction and decreased medullary blood flow as a result of the viscosity of the contrast leading to ischemia. In addition, contrast is directly cytotoxic to the renal tubular cells, causing further tubular injury.

DIAGNOSTIC CRITERIA FOR CONTRAST-INDUCED ACUTE KIDNEY INJURY

AKI is defined by updated Kidney Disease Improving Global Outcomes criteria as an absolute increase in serum creatinine of at least 0.3 mg/dL or greater than 1.5 times the baseline creatinine or a decrease in urine output to less than 0.5 mL/kg/h for at least 6 hours. When AKI occurs within 48 hours of contrast administration and other causes of AKI can be ruled out, it is labeled as CI-AKI. However, this definition is fraught with problems because exclusion of other causes is often impossible. Therefore, a new term of “contrast-associated AKI” (CA-AKI) was adopted to describe any AKI that occurs within 48 hours of contrast administration. This term removes the implied causality of contrast causing AKI because most studies describing CI-AKI failed to establish that contrast was indeed the only factor responsible for the development of AKI. On the other hand, the term “CI-AKI” refers to the subset of CA-AKI that can be causally linked to contrast media administration.

RISK FACTORS FOR CONTRAST-INDUCED ACUTE KIDNEY INJURY

There are multiple risk factors that can predispose patients to CI-AKI, which can be broadly categorized into patient-related and contrast-related risk factors.

Preexisting Chronic Kidney Disease

The risk of CI-AKI increases linearly with the decline in glomerular filtration rate (GFR), but an exact cutoff at which the risk increases has been hard to define. One study shows that up to 4.2% of patients with an estimated GFR of 30 to 59 mL/min/1.73 m² developed AKI after intra-arterial contrast administration. Another study of patients with severe CKD shows that in patients with a serum creatinine greater than 3 mg/dL (which would signify a GFR <30 mL/min/1.73 m²), there is a 31% risk of AKI after contrast administration for percutaneous coronary intervention (PCI). However, a more recent study of more than 12,000 patients has shown a lower risk of 14% of developing AKI in patients with a GFR of less than 30 mL/min/1.73 m² after receiving contrast for a computed tomography scan. One of the most interesting findings from this study is that the propensity score–matched cohort of patients with an estimated GFR less than 30 mL/min/1.73 m² who did not receive contrast had the same incidence of AKI. This has raised serious doubts about the culpability of contrast in causing AKI.

Regardless of the conflicting results from different studies, given the high incidence of AKI in patients with GFR less than 30 mL/min/1.73 m², a discussion of risk and benefits of contrast administration should occur with the patient before proceeding with contrast administration.

Diabetes Mellitus

Patients with diabetic CKD are at a higher risk of developing CI-AKI compared with patients with nondiabetic CKD, but diabetes alone in the absence of CKD does not increase the risk of CI-AKI.

Type of Contrast Used

High-osmolality contrast media were one of the first agents to be used but have fallen out of favor because they are more nephrotoxic than the newer agents. Low-osmolality contrast agents (LOCMs) such as iohexol, iopamidol, ioversol, andioxaglate are presently the most widely used agents that have a lower osmolality than high-osmolality contrast media but are still hyperosmolar (~600 mOsm/kg). Iodixanol is the only commercially available agent with an osmolality of approximately 290 mOsm/kg. Theoretically, the risk of kidney injury should be lower with iso-osmolality contrast media (IOMC); however, one study showed only a slight decrease in the risk of CI-AKI using iodixanol compared with LOCM (pooled relative risk, 0.80 [95% confidence interval, 0.65-0.99]; P = .045). One possible explanation for this result is the dimeric structure of IOMC that makes them more viscous than LOCM; therefore, a significant difference in the risk of CI-AKI is not seen.

Intra-arterial versus Intravenous Contrast

Given that coronary angiography is associated with higher risk of CA-AKI compared with contrast-enhanced computed topography scan, some have argued that intra-
arterial administration of contrast is more nephrotoxic than intravenous (IV) administration given increased exposure of the kidneys to the contrast. Intra-arterial administration of contrast will present a higher concentration of the contrast to the renal arteries compared with IV administration only if the contrast is given in the aorta above or at the level of the renal artery, which can be seen with left ventriculography or aortograms. Therefore, it seems that other factors such as the patient’s comorbid conditions, inherent procedural risks of angiography (hemorrhage, atheroemboli), and higher doses of contrast used in coronary angiography are more likely to be responsible for the higher rates of CA-AKI seen than the direct arterial administration of contrast. One study compared the incidence of AKI after IV and intra-arterial contrast in the same patient and did not show a significant difference in the rate of AKI based on the route of contrast administration. In summary, intra-arterial procedures that involve imaging of the aorta at or above the renal arteries increase contrast to the kidneys leading to increased risk of CI-AKI because of direct contrast exposure. Complications from the intra-arterial procedure (hemorrhage, atheroemboli to the kidney) may increase AKI risk independent of the CI-AKI.

Risk Calculator for Contrast-Induced Acute Kidney Injury Undergoing Percutaneous Coronary Intervention

To discuss the potential risks of contrast administration with the patients, clinicians often need to estimate the risk of developing CI-AKI. On the basis of a study of more than 8000 patients, Mehran and colleagues have developed a risk score calculator for prediction of CI-AKI in patients undergoing PCI. The variables included are the baseline demographics, preexisting chronic severity of illness, and amount of contrast used. The calculator can be found online at https://qxmd.com/calculate/calculator_47/contrast-nephropathy-post-pci.

PREVENTION OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

It is important to recognize patients who are at high risk of CI-AKI, such as patients with severe CKD (estimated GFR <30 mL/min/1.73 m²) or moderate renal dysfunction (estimated GFR <45 mL/min/1.73 m²) in the presence of other comorbidities such as diabetes, heart failure, or liver failure. Every effort should be made to decrease the risk of CI-AKI by considering the following factors.

Type of Contrast Used

IOM (iodaxinol) or nonionic LOCM (eg, iopamidol or ioversol) should be used preferentially in patients at risk of developing CI-AKI.

Dose of Contrast Used

The risk of developing CI-AKI is dependent on the amount of contrast used. There is no absolute cutoff below which contrast is completely safe, but the incidence of CI-AKI is rare with less than 100 mL of contrast. The minimum amount of contrast possible should be used in at-risk patients, and repeated studies within the 48- to 72-hour period should be avoided.

Intravenous Fluids

Volume expansion with IV fluids before administration of contrast has been shown to decrease the risk of CI-AKI. It potentially dilutes the contrast and attenuates the cytotoxic effects and improves overall hemodynamics of the patient unless the patient is hypervolemic. Therefore, all patients who are at high risk for developing CI-AKI should receive prophylactic IV fluids in the absence of a contraindication such as heart failure or other causes of hypervolemia. In a trial of 408 patients with acute myocardial infarction undergoing percutaneous coronary angiography, most of whom had normal kidney function, IV saline reduced the risk of contrast nephropathy compared with no saline (11% vs 21%). In comparison, another randomized trial found no benefit of IV saline compared with no saline in preventing AKI among 603 patients with estimated GFR between 30 and 59 mL/min/1.73 m². Therefore, the data on the efficacy of volume expansion are not consistent, but given the lack of evidence behind other preventive strategies, volume expansion remains the cornerstone of CI-AKI prevention.

The type of fluid that should be used has been a matter of debate in the past, with some studies demonstrating superior results with the use of isotonic sodium bicarbonate over normal saline. However, more recent randomized controlled trials have not shown any benefit of using sodium bicarbonate over normal saline. Given that sodium bicarbonate has to be compounded by a pharmacist and is more expensive, normal saline is the recommended fluid for these patients.

The ideal timing, amount, and rate of IV fluid administration are also debatable, and different institutions have developed local protocols for this. One outpatient IV fluid protocol involves giving 3 mL/kg/h of fluid for 1 hour preprocedure and 1 to 1.5 mL/kg/h for 4 to 6 hours afterward. Inpatients should receive IV fluids for a longer duration with 1 mL/kg/hour given 6 hours preprocedure, intraprocedurally, and for 6 to 12 hours postprocedure.

N-Acetyl Cysteine

Because reactive oxygen species play a role in the pathogenesis of CI-AKI, it seems plausible that an antioxidant such as N-acetyl cysteine (NAC) may be beneficial in preventing CI-AKI. Although NAC is inexpensive and mostly...
well tolerated by patients, there are some potential rare side effects of using NAC, such as depressed cardiac function.\textsuperscript{25} There have been conflicting data regarding the efficacy of NAC in preventing CI-AKI, but a recent randomized controlled trial of 4993 patients undergoing angiography showed no benefit of using oral NAC in the prevention of CI-AKI in patients undergoing angiography, and its use is no longer recommended.\textsuperscript{24}

**Withholding Medications**

Certain nephrotoxic medications such as nonsteroidal anti-inflammatory drugs should be withheld for 48 hours before contrast administration because they cause renal vasoconstriction and can further reduce the blood flow to the kidneys.

The role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the pathogenesis of CI-AKI is controversial. In one study, ACEI/ARB users showed an increased incidence of CI-AKI compared with a propensity score–matched cohort (11.4\% vs 6.3\%; \( P < .001 \)).\textsuperscript{26} A study of more than 200 patients did not show a benefit of holding ACEIs and ARBs before contrast administration.\textsuperscript{27} On the other hand, a meta-analysis of more than 4400 patients showed that the continuation of ACEI/ARB was associated with a higher incidence of CI-AKI compared with discontinuation (odds ratio, 2.06; 95\% confidence interval, 1.62-2.61; \( P < .001 \)) in chronic ACEI and ARB users.\textsuperscript{28} Given this, the recent American College of Radiology and National Kidney Foundation guidelines on IV contrast risks have suggested that withholding these medications should be considered.\textsuperscript{11}

Patients’ home diuretic dose should be continued unless there is concern for hypovolemia. There has been no consistently demonstrated efficacy of prophylactic diuretic use or forced diuresis.

Metformin does not increase the risk of CI-AKI, but the risk of lactic acidosis is higher if patients develop CI-AKI, so it should be held in patients who have an AKI or a GFR less than 30 mL/min/1.73 m\(^2\) on the day of contrast administration. The US Food and Drug Administration also recommends withholding metformin before iodinated contrast media exposure for estimated GFR 30 to 59 mL/min per 1.73 m\(^2\); however, because the risk of CI-AKI is low at that level, an individual assessment of risk and benefits should be made before making a decision of withholding metformin. Metformin can be resumed after 48 hours if the kidney function remains stable; however, if development of CI-AKI occurs, then metformin should be held until the resolution of AKI.

**Hemodialysis**

Performing hemodialysis immediately to remove contrast has no role in the prevention of CI-AKI.\textsuperscript{29,30}

**PROGNOSIS OF CONTRAST-INDUCED ACUTE KIDNEY INJURY**

In most cases of CI-AKI, creatinine starts trending down in 3 to 7 days and returns to baseline in the majority of patients.\textsuperscript{31} In a study of 21 patients aged more than 70 years with CI-AKI, 57\% had complete recovery and 19\% had partial recovery within 5 to 7 days.\textsuperscript{31} In general, CI-AKI is not severe enough to require dialysis, and in one study of more than 1800 patients, the incidence of dialysis requiring CI-AKI was less than 1\%.\textsuperscript{15} However, patients who have advanced CKD at baseline will have a higher risk of requiring dialysis.

In addition, CI-AKI is associated with an increased long-term mortality. In a study of more than 9000 patients undergoing PCI, CI-AKI was associated with a higher 30-day (4.9\% vs 0.7\%; \( P < .0001 \)) and 1-year (9.8\% vs 2.9\%; \( P < .0001 \)) mortality.\textsuperscript{32} However, this showed an association and not causality because it is likely that despite adjustments there were inherent differences in the patients who developed CI-AKI compared with those who did not.

**FUTURE DIRECTIONS**

One of the major pitfalls of diagnosing CI-AKI on the basis of the current criteria is that it relies on serum creatinine for diagnosis. Serum creatinine is a poor marker to evaluate the effect of any nephrotoxic agent because there is a lag between the insult and the actual increase. Given these limitations, there is tremendous interest in using biomarkers that can detect AKI earlier, allowing for earlier intervention. Neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 are 2 such biomarkers that are upregulated in the setting of proximal tubular injury and might prove to be useful in the early detection of CI-AKI.\textsuperscript{33} In addition, renal tubular damage, in particular DNA damage, can cause cell cycle arrest. Cell cycle inhibitors, tissue inhibitor metalloproteinase-2, and insulin-like growth factor-binding protein 7 are upregulated as a result and have been identified as biomarkers for the prediction of AKI risk.\textsuperscript{34} The Food and Drug Administration has approved a point-of-care device for the measurement of these 2 biomarkers. Future studies need to focus on the ideal timing and frequency of these biomarker measurements in the setting of CI-AKI. Ideally, a biomarker would also distinguish CI-AKI from other concurrent causes, such as hemodynamic instability, and therefore would help in determining the true incidence of CI-AKI.

Another issue that should be addressed with a well-designed trial is whether ACEIs and ARBs should be discontinued before contrast administration given conflicting results from prior studies.

**CONCLUSIONS**

Most studies show that CI-AKI has been overdiagnosed in patients with acute illness and exposure to multiple other
ever, those with a GFR less than 30 mL/min/1.73 m² are at risk of developing CI-AKI. These patients should receive preprocedure IV saline in the absence of a contraindication and the minimal amount of LOCM or IOCM agents without sacrificing image quality to decrease the risk of CI-AKI (Figure 1).

Conflict of Interest Statement
The authors reported no conflicts of interest.

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