Inpatient Notes: Preventing Contrast-Associated Acute Kidney Injury–Putting the Issue to Rest

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It has long been recognized that intravascular administration of iodinated contrast can precipitate an abrupt decline in kidney function, particularly among patients with underlying chronic kidney disease (CKD). This iatrogenic complication, contrast-associated acute kidney injury (CA-AKI), has been associated with increased risk for serious adverse outcomes, including short- and long-term mortality, progressive decline in kidney function, and need for dialysis. However, these observed associations, which derive principally from retrospective observational studies, have not been confirmed to be causal. Most commonly defined by small increments in serum creatinine levels, CA-AKI may simply be a marker for, rather than a mediator of, these adverse outcomes. Regardless, providers' fear of precipitating CA-AKI is believed to be at least part of the reason that patients with CKD are considerably less likely than those without CKD to undergo clinically indicated contrast-enhanced procedures for such conditions as acute coronary syndrome. The seminal study of this phenomenon by Chertow and colleagues (1) reported that patients hospitalized with acute myocardial infarction who had CKD were approximately 50% less likely to undergo coronary angiography than those without. Moreover, patients with CKD who had angiography were half as likely to die in the next 12 months than those who did not. Given these findings, which have been replicated in other studies, as well as the absence of data confirming a causal association of CA-AKI with adverse outcomes, clinically indicated diagnostic and interventional procedures that require intravascular iodinated contrast should be done in patients with CKD, albeit with implementation of evidence-based preventive care.

What Constitutes Evidence-Based Preventive Care?

Over the past 2 decades, the 2 interventions that have been studied most intensively for prevention of CA-AKI are *N*-acetylcysteine (NAC), a vasodilatory antioxidant, and intravenous isotonic sodium bicarbonate. Initial interest in the former stemmed from the results of a clinical trial by Tepel and coworkers (2) that randomly assigned 83 patients with CKD having contrast-enhanced computed tomography to receive 2 days of oral NAC (n = 41) or oral placebo (n = 42). Compared with placebo, NAC was associated with reduced risk for CA-AKI, defined by an increase in serum creatinine of 0.5 mg/dL or greater 48 hours after contrast administration (relative risk, 0.1 [95% CI, 0.02 to 0.9]; P = 0.01). However, over the ensuing years numerous randomized clinical trials of NAC and subsequent meta-analyses yielded conflicting results.

Similarly, the focus on intravenous isotonic sodium bicarbonate (as compared with intravenous isotonic saline) began with publication of a randomized clinical trial in 2004 by Merten and colleagues (3). This trial enrolled 119 patients having procedures with intravascular iodinated contrast and reported a lower incidence of CA-AKI in patients who received sodium bicarbonate than those who received saline (1.7% vs. 13.6%; P = 0.02). Similar to NAC, the results of subsequent clinical trials and meta-analyses were inconsistent and inconclusive.

Failure to clearly define the role of NAC and sodium bicarbonate for the prevention of CA-AKI over a nearly 20-year period resulted primarily from methodological limitations of the myriad clinical trials. Nearly all had small sample sizes and limited statistical power. Most used primary end points defined by small, short-term changes in serum creatinine levels rather than more clinically meaningful outcomes, such as death or progressive deterioration in kidney function, which would have required considerably larger sample sizes. Finally, many enrolled low-risk patients, making it harder to detect any effect from the treatments.

Despite the inability of these trials to establish evidence-based strategies for the prevention of CA-AKI, they provided justification for the design and conduct of the PRESERVE (Prevention of Serious Adverse Events Following Angiography) trial (4). PRESERVE was a multinational placebo and comparator-drug–controlled trial that used a 2 x 2 design in 4993 randomly assigned patients with CKD having nonemergent angiography. The interventions were 5 days of oral NAC or matching placebo, as well as periprocedural intravenous isotonic sodium bicarbonate or intravenous isotonic saline (5). The primary outcome was a composite 90-day end point comprising death, need for dialysis, or persistent kidney impairment; CA-AKI was a secondary outcome. The trial found that NAC was not associated with decreased risk for the primary end point (odds ratio [OR], 1.02 [CI, 0.78 to 1.33]) or CA-AKI (OR, 1.06 [CI, 0.87 to 1.28]) compared with placebo. Similarly, compared with saline, sodium bicarbonate was not associated with a decreased risk for the primary outcome (OR, 0.93 [CI, 0.72 to 1.22]) or for CA-AKI (OR, 1.16 [CI, 0.96 to 1.41]). In addition to providing the evidence necessary to establish intravenous isotonic saline without NAC as the standard of prevention in high-risk patients, PRESERVE underscored the pitfalls of relying on small trials with primary end points of unclear clinical significance and with limited statistical power to investigate patient-centered outcomes to inform the standard of care.

RECOMMENDATIONS FOR HOSPITALISTS

Hospitalists caring for patients at elevated risk for CA-AKI should implement evidence-based preventive care when administration of intravascular iodinated contrast is necessary. This includes pre-, intra-, and postprocedure intravenous isotonic saline; discontinuation of concomitant nephrotoxins (for example, nonsteroidal anti-inflammatory drugs); use of the lowest possible volume of contrast; and avoidance of multiple sequential contrast-enhanced procedures. In lieu of further small underpowered trials that use surrogate end points, the performance of adequately powered trials of other potential interventions focused on the prevention of serious, adverse, patient-centered outcomes are necessary to further advance this field.

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