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In the Literature

Prevention of Contrast-Associated Acute Kidney Injury: What Should We Do?

Commentary on Eng J, Wilson RF, Subramaniam RM, et al. Comparative effect of contrast media type on the incidence of contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med. *2016;164(6):417-424, and Subramaniam RM, Suarez-Cuervo C, Wilson RF, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis.* Ann Intern Med. *2016;164(6):406-416.*

Contrast-associated acute kidney injury (AKI) is a common iatrogenic complication associated with increased health resource utilization and adverse outcomes, including short- and long-term mortality and accelerated progression of underlying chronic kidney disease (CKD). Although the causal nature of these associations is not established, these findings underlie past and ongoing efforts to identify interventions to reduce patients' risks for this condition. Contrast-associated AKI is potentially preventable because high-risk patients often are identifiable by the presence of underlying comorbid conditions such as CKD, the precise timing of the kidney insult is known in advance, and most contrast-enhanced procedures are performed nonemergently with ample time to implement prophylactic measures. Early studies confirmed that use of low-osmolal contrast media (osmolality 2-3 times that of plasma) compared with high-osmolal contrast media (osmolality $>$ 4 times that of plasma) and the administration of periprocedural intravenous (IV) isotonic crystalloid both reduce the risk for contrast-associated AKI in at-risk patients.[1-3] More recent clinical trials that compared newer generation contrast agents; evaluated pharmacological interventions, including antioxidants and statins; and investigated IV crystalloid solutions containing bicarbonate have yielded conflicting findings. This led to efforts to systematically examine trial results using meta-analyses.

WHAT DO THESE STUDIES SHOW?

Two recently published meta-analyses[4,5] based on comparative effectiveness reviews prepared for the Agency for Healthcare Research and Quality (AHRQ)[6,7] evaluated interventions for the prevention of contrast-associated AKI. Key findings of the studies are summarized in Box 1. In the first study, Eng et al[4] examine clinical trials that compared different low-osmolal contrast media and that compared iso-osmolal iodixanol with low-osmolal contrast media. Each trial was assessed for risk of bias and all pooled comparisons were graded on their strength of evidence, ranging from insufficient to high. The investigators assessed each comparison for clinical importance, defined a priori as a point estimate of the reduction in risk for contrast-associated AKI of no less than 25% (ie, risk ratio [RR] $\leq$ 0.75) and statistical significance, assessed based on whether the 95% confidence interval (CI) excluded a pooled RR of 1.0.

Twenty-nine trials were included in this meta-analysis, of which 5 (826 patients) compared different low-osmolal contrast media and 25 (5,053 patients) compared iodixanol with low-osmolal contrast media. The investigators found that none of the trials comparing low-osmolal contrast media demonstrated statistically significant or clinically important differences in effect, while reporting low strength of evidence for these comparisons. Of 25 trials comparing iodixanol with low-osmolal contrast media, 2 were omitted due to the absence of a clear definition of contrast-associated AKI. The other 23 trials collectively demonstrated a statistically significant, yet clinically unimportant, reduction in risk for contrast-associated AKI with iodixanol (RR = 0.80; 95% CI, 0.65-0.99). Subgroup analyses based on route of contrast administration, dose of contrast, and underlying patient characteristics found no benefit to iodixanol. The investigators concluded that there was no difference in risk for contrast-associated AKI among low-osmolal contrast media and that despite finding a statistically significant reduction in risk for contrast-associated AKI with iodixanol, the observed point estimate of the reduction in relative risk (20%) did not exceed the 25% minimal threshold for clinical importance.

The second study by Subramaniam et al[5] examines the efficacy of *N*-acetylcysteine (NAC), statins, sodium bicarbonate, and ascorbic acid in mitigating contrast-associated AKI risk. Overall, 86 clinical trials were included, 54 of which compared NAC along with IV saline to IV saline with or without placebo. The investigators reported that low-dose NAC (RR = 0.75; 95% CI, 0.63-0.89) and NAC in the setting of low-osmolal contrast media use (RR = 0.69; 95% CI, 0.58-0.84) were associated with

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Box 1. Key Findings of Meta-analyses of Prevention Strategies for Contrast-Associated AKI

Type of contrast media
- There were no differences in risk for contrast-associated AKI associated with different types of low-osmolal contrast media
- Iodixanol was associated with a non–clinically significant reduction in risk for contrast-associated AKI as compared, in aggregate, with low-osmolal contrast media

NAC
- In patients receiving intravenous saline, NAC was associated with a reduction in risk for contrast-associated AKI when low-osmolal contrast media were used, but not when iodixanol was the contrast medium used
- In patients receiving intravenous saline, low-dose NAC was associated with a borderline clinically significant reduction in risk for contrast-associated AKI, regardless of type of contrast media used
- In patients receiving intravenous saline, high-dose NAC was not associated with reduction in risk for contrast-associated AKI, regardless of type of contrast media used

Intravenous sodium bicarbonate
- Intravenous sodium bicarbonate as compared to intravenous saline was not associated with a reduction in risk for contrast-associated AKI

Statins
- In patients receiving both intravenous crystalloid and NAC, statins were associated with a clinically significant reduction in risk for contrast-associated AKI
- In patients receiving intravenous saline without NAC, statins were not associated with a reduction in risk for contrast-associated AKI

Ascorbic Acid
- In patients receiving intravenous saline, ascorbic acid was not associated with reduction in risk for contrast-associated AKI

Abbreviations: AKI, acute kidney injury; NAC, *N*-acetylcysteine.
Source: Eng et al[4] and Subramaniam et al.[5]

reductions in risk for contrast-associated AKI, whereas low-dose NAC with intra-arterial contrast administration (RR = 0.77; 95% CI, 0.66-0.91) and oral NAC (RR = 0.77; 95% CI, 0.65-0.92) were associated with "clinically unimportant" but statistically significant reductions in risk. No benefit was found for high-dose NAC, low-dose NAC with IV contrast administration, IV NAC, or NAC in the setting of iodixanol use. The strength of evidence for most comparisons was low.

Pooling 19 trials, the investigators found that IV sodium bicarbonate was not associated with reduction in risk for contrast-associated AKI (RR = 0.93; 95% CI, 0.68-1.27), with low strength of evidence. The use of statins (with IV crystalloid) was associated with a clinically important but non–statistically significant reduction in risk (RR = 0.68; 95% CI, 0.39-1.20) in 8 studies with low strength of evidence. In 5 studies that evaluated statins in addition to NAC and IV crystalloid, statins were associated with a reduction in risk for contrast-associated AKI (RR = 0.52; 95% CI, 0.29-0.93). Finally, in the setting of IV crystalloid administration, ascorbic acid was associated with a clinically important but non–statistically significant reduction in risk (RR = 0.72; 95% CI, 0.48-1.01). The investigators concluded that the largest reduction in risk for contrast-associated AKI was with NAC among patients receiving low-osmolal contrast media and with statins administered with NAC.

These meta-analyses have important limitations. While acknowledged by the authors, Eng et al considered all low-osmolal contrast media collectively despite prior studies suggesting that iohexol may be associated with increased nephrotoxicity compared with other low-osmolal agents.[8,9] Furthermore, nearly half the 29 trials overall and 4 of the 5 trials comparing low-osmolal contrast media enrolled patients without underlying CKD and thus with relatively low risk for contrast-associated AKI, biasing analyses toward the null. In addition, differences across trials in use, dose, and timing of administration of other potentially preventive interventions such as NAC and IV fluids could not be fully accounted for in this meta-analysis. A notable proportion of trials included in the analysis by Subramaniam et al also enrolled patients without CKD, which predisposed the pooled analyses to finding no benefit. Moreover, Subramaniam et al reported a benefit with low-dose NAC that was not seen with high-dose NAC, a finding that lacks biological plausibility and likely reflects the larger size and greater methodological rigor of trials that used high-dose NAC.[10]

Other caveats common to both meta-analyses also warrant consideration. First, most comparisons had low strength of evidence related to the low quality of the included clinical trials, almost all of which enrolled small numbers of patients. These trials were designed based on implausibly large postulated effect sizes and therefore had very limited statistical power.[11] Second, none of the interventions reduced clinically important outcomes such as need for dialysis therapy, mortality, or cardiac events. Although small increments in serum creatinine levels used to define contrast-associated AKI have been associated with subsequent mortality and persistent decline in kidney function, the causal nature of these associations is not established. Finally, the arbitrary definition of clinical importance based exclusively on the point estimate of risk reduction (≥25%) without considering the CI is potentially misleading. For example, an intervention with a point estimate for the RR of contrast-associated AKI of 0.76 with a narrow CI (eg, 0.72-0.80) would be labeled clinically unimportant, whereas an intervention with a slightly lower

point estimate of 0.74 but a much wider CI (eg, 0.49-0.99) would be deemed clinically important.

Importantly, several of the interventions analyzed in the study by Subramaniam et al are imprecisely described in both the AHRQ Comparative Effectiveness Review[7] and the *Annals of Internal Medicine* article.[5] Although IV crystalloid was administered in both the treatment and control arms in all included clinical trials, the comparisons are variably characterized as NAC, statin, or ascorbic acid versus IV saline, suggesting that these agents can be administered in lieu of IV crystalloid, which is not the case.

HOW DO THESE STUDIES COMPARE WITH PRIOR STUDIES?

During the past decade, several meta-analyses have compared iodixanol with low-osmolal contrast media for the prevention of contrast-associated AKI.[8,9,12-14] Two studies reported finding no statistically significant differences; one found a statistically significant benefit to iodixanol, particularly in patients with CKD, and one found no difference overall but noted significant heterogeneity among trials that included patients with kidney disease who received intra-arterial contrast. Specifically, the effect differed when trials using iohexol were segregated from trials comparing other low-osmolal contrast media to iodixanol.[8] In this analysis, although there was no difference in risk for contrast-associated AKI observed when iodixanol was compared with low-osmolal contrast media other than iohexol (RR = 0.97; 95% CI, 0.72-1.32), the RR was notably lower (RR = 0.45; 95% CI, 0.26-0.76) in the pooled analysis of 5 trials comparing iodixanol to iohexol. Additionally, a network meta-analysis that included 42 trials with more than 10,000 patients found that iohexol and ioxaglate were associated with increased risk for contrast-associated AKI compared with iodixanol and 4 other low-osmolal contrast media.[9] These findings contrast with the interpretation by Eng et al, which described the evidence of greater risk with iohexol as "indirect" and consequently analyzed all low-osmolal contrast media collectively.

Remarkably, there have been more than 20 meta-analyses examining the effect of NAC on contrast-associated AKI, a similar number examining the effect of statins on contrast-associated AKI, and more than 15 evaluating sodium bicarbonate for the prevention of contrast-associated AKI.[15,16] The findings of these meta-analyses are as conflicting as results of the clinical trials upon which they are based. Although the current meta-analysis by Subramaniam et al used slightly different methodological approaches and analytic techniques from the prior analyses, the considerable overlap of included trials and low quality of the primary data explain the inability for these analyses to determine the true benefit, if any, of these interventions.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The literature is replete with methodologically flawed and inadequately powered trials that have largely failed to inform the use of evidence-based care for the prevention of contrast-associated AKI. Although systematic reviews and meta-analyses represent the pinnacle of the evidence-based medicine hierarchy, their value is dependent on the quality of the primary trials upon which they are based. Consequently, despite numerous meta-analyses, equipoise persists with regard to the role of most interventions for the prevention of contrast-associated AKI because the primary trials are largely of low quality with significant methodological limitations. At the same time, a growing number of observational analyses have documented the underutilization of coronary angiography in patients with CKD, at least in part out of concern for the development of contrast-associated AKI, a phenomenon aptly labeled renalism.[17,18] This observation is particularly notable given that cardiovascular disease is the leading cause of death in patients with CKD, whereas the associations of contrast-associated AKI, defined by small increments in blood creatinine levels, with serious patient-centered outcomes have yet to be proved causal. It is therefore imperative that clinicians appreciate the limitations in research to date related to various interventions for the prevention of contrast-associated AKI; understand that the administration of periprocedural IV isotonic crystalloid, the use of either iodixanol or low-osmolal contrast media, and avoidance of concomitant nephrotoxins such as nonsteroidal anti-inflammatory drugs are effective evidence-based interventions; and ensure that patients with CKD who have clear indications for contrast-enhanced procedures undergo these procedures, albeit with appropriate use of evidence-based preventive care.

It is similarly important for researchers to appreciate why the multiple trials and meta-analyses of interventions to prevent contrast-associated AKI have yielded limited meaningful data. The conduct of small inadequately powered trials focused on small short-term changes in serum creatinine levels rather than more important clinical outcomes has fueled the proliferation of meta-analyses that are unable to generate consistent convincing results. Large adequately powered clinical trials that enroll high-risk patients and evaluate more meaningful outcomes, such as persistent decline in kidney function, need for

dialysis, and death, are essential to move this field forward.

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