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Discord Over Contrast-Induced Nephropathy

Pam Harrison

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WASHINGTON, DC — Contrast-induced nephropathy "has been medical dogma for decades," but some physicians, like Jennifer McDonald, PhD, associate professor of radiology at the Mayo Clinic in Rochester, Minnesota, are not convinced that it exists.

Jennifer McDonald

After researching the subject for the past 8 or 9 years, McDonald said she remains unconvinced that intravenous (IV) low-osmolality iodinated contrast material causes acute kidney injury.

McDonald, who is a scientific advisor for GE Healthcare, the manufacturer of a variety of contrast media products, will present evidence at the upcoming Kidney Week 2019.

"Most studies that have demonstrated a physiological change in the kidney after contrast was used were animal models," she told *Medscape Medial News*. And those animals had purposely been subjected to severe renal insults prior to the administration of contrast media or were given massive doses of high-osmolality contrast agents that are no longer used in medical practice.

The larger point is that "only a handful" of studies that have looked at contrast-induced nephropathy in humans "have included a control group of patients not given contrast," said McDonald, meaning that the studies were uncontrolled and all subsequent cases of kidney injury were blamed on the contrast media.

Unfair Blame

This is really unfair given that any of the many causes of acute kidney injury — including dehydration, sepsis, hypotension, and nephrotoxic drugs — could have been the culprit in these uncontrolled studies, she explained.

Furthermore, contrast-induced nephropathy is defined by a change in serum creatinine after the administration of contrast media.

However, it has been shown that the increase in creatinine levels is similar in patients who receive contrast media and those who do not. So serum creatinine, which is subject to natural fluctuations in the absence of any contrast media, is a poor marker of kidney injury, said McDonald.

In addition, a meta-analysis of more than 100,000 patients involved in controlled studies showed that there are no significant associations between contrast-enhanced CT and kidney injury, the need for renal replacement therapy, or all-cause mortality.

But "we know that there are good clinical reasons to give contrast," McDonald added. "If it's clinically indicated to do a coronary angiography with contrast, it's really important to do these procedures to diagnose entities such as cancer, to monitor patients, and to screen things over time."

"I think that in the vast majority of patients who develop acute kidney injury, there is a transient bump in the

creatinine, but it's generally resolved in 7 days," she said.

Overestimated, But Real

Rates of contrast-induced nephropathy are likely overestimated, according to a study by Glenn Chertow, MD, professor of medicine at the Stanford University School of Medicine in Palo Alto, California, and colleagues.

Chertow and his team projected the risk for radiocontrast-associated nephropathy in almost 6 million patients using the Nationwide Inpatient Sample. When they controlled for the presence and absence of the most common diagnoses associated with acute kidney injury and the degree of pre-existing comorbidity in their large cohort, they found that rates of injury were similar in patients who did and did not receive a radiocontrast agent (5.5% vs 5.6%).

After adjustment for age, sex, mechanical ventilation, and combined comorbidity score, rates of injury were actually lower in the group that received contrast media than in the group that did not (5.1% vs 5.6%).

This finding that has been confirmed in other studies, such as a meta-analysis that showed no association between contrast-enhanced CT and acute kidney injury (odds ratio [OR], 0.94), need for renal replacement therapy (OR, 0.83), or all-cause mortality (OR, 1.0).

But this does not mean that contrast-induced nephropathy does not exist; in fact, Chertow will argue the case for an association between contrast media and kidney injury at the upcoming meeting.

Unless it can be argued that contrast is nephroprotective — and it absolutely cannot — the reason for the discrepancy could be that if a patient has poor kidney function or is simply very sick, the provider might suspect that the contrast agent will not be well tolerated and will not order it, he and his colleagues suggest.

Indication Bias

Steven Weisbord

Propensity-score matching is a statistical method used to level the playing field between two groups, but "no degree of propensity matching or retrospective adjustment for covariates is going to eliminate that bias by indication, and that is why you still see statistically significant or strong trends toward lower rates of acute kidney injury in patients who receive contrast, because they are less sick [than those who do not]," said Steven Weisbord, MD, professor of medicine at the University of Pittsburgh School of Medicine.

An observed dose–response relationship between the contrast volume administered and the risk for renal injury supports the notion that these agents have the potential to be nephrotoxic, Weisbord pointed out in an editorial last year.

"While secular trends including the use of lower volumes of less nephrotoxic contrast along with the widespread use of preventive care including intravascular volume expansion have likely contributed to decreased rates of contrast-associated acute kidney injury and rendered severe renal injury a relatively rare complication of contrast administration alone, these factors have not eliminated the existence of this iatrogenic condition," Weisbord and his colleague write.

"Continued vigilance and appropriation of evidence-based preventive care in the highest risk patients remains essential," they conclude.

Preventing Injury

Although most episodes of kidney injury resolve on their own, they can nevertheless be serious. Those who develop it are at risk for loss of kidney function and the need for dialysis.

"Whether the acute kidney injury is a mediator of those outcomes or whether it is just a marker of patients who are at higher baseline risk for those outcomes, one needs to assume that there is a potential for these serious outcomes associated with acute kidney injury and administer appropriate, evidence-based preventive care," said Weisbord, who is a consultant for Saghmos Therapeutics, a privately held biopharmaceutical company with a mission to prevent and treat kidney injury due to contrast dyes.

For patients deemed to be at elated risk for kidney injury, IV isotonic sodium chloride is really the cornerstone of preventive care, he told *Medscape Medical News*.

In a study looking at whether sodium bicarbonate or oral acetylcysteine — widely used to prevent kidney injury and adverse outcomes after angiography — offer protection against injury, Weisbord and his colleagues determined that they do not.

Overall, there are few data on the use of IV fluids.

In the phase 3 AMACING study comparing IV fluids with no fluids, rates of contrast-induced nephropathy were similar in hydrated and unhydrated patients (2.7% vs 2.6%).

"The issue with that study is that it enrolled primarily a low-risk population, so most patients had relatively well-preserved kidney function and underwent CT scan, not angiography, which accounts for the finding of no difference between the two groups," Weisbord explained.

That does not rule out the possibility that patients at high risk for kidney injury might still benefit from them, he added.

Preferential use of low-osmolar over high-osmolar contrast media appears to reduce the risk for contrast-induced injury, Weisbord pointed out.

And the risk for nephropathy induced by a contrast agent might be lower when iodixanol (*Visipaque*, GE Healthcare) is administered instead of a low-osmolar, nonionic contrast medium, at least in patients undergoing angiography, according to one study.

It is noteworthy, however, that recommendations from many societies do not differentiate between low-osmolar and iso-osmolar contrast media with regard to the risk for kidney injury, Weisbord explained.

For patients who really need a contrast-enhanced procedure, nephrologists should minimize contrast volume and avoid sequential procedures done over a short period of time, he advised.

Kidney Week 2019: American Society of Nephrology Annual Meeting. Presentation November 9, 2019.

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