Editorial

Diagnosing and treating contrast-induced acute kidney injury in 2017

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Comment on: Nijssen EC, Rennenberg RJ, Nelemans PJ, *et al.* Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet 2017;389:1312-22.

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Contrast-induced acute kidney injury (CI-AKI) is an important complication of intravascular administration of contrast media required in many diagnostic and therapeutic procedures across a variety of medical and surgical disciplines. It is classified as an etiology of acute kidney injury (AKI) but specifically only refers to AKI as a result of intravascular contrast use. CI-AKI is usually defined as a rise in serum creatinine (SCr) of 0.5 mg/dL (44 μmol/L) or a 25% increase from baseline value 48 h after administration of contrast (1). In patients with baseline normal renal function it has been accepted that the risk of CI-AKI is low (1–2%) (2). However, in older patients with pre-existing medical comorbidities including underlying baseline renal impairment, diabetes, and congestive heart failure; the risk of CI-AKI is around 25% (2). Importantly, CI-AKI is described as third most common cause of AKI in hospitalized patients (after decreased renal perfusion and nephrotoxic medications) and accounts for 15% of AKI clinical cases (3). It is now known patients who develop CI-AKI have longer hospitalizations, increased early and late cardiovascular events, and higher mortality compared to patients with normal renal function. The pathophysiology of CI-AKI has not been elucidated and thus clinically targeted pharmacotherapy has not been achieved. Therefore, the focus has been on assessment of overall risk for CI-AKI prior to contrast administration, identifying potential novel ways to change contrast formulation, and primarily focusing on prevention related therapies. Non-pharmacological prevention strategies have suggested low dose iso-osmolar contrast administration in replacement of high-osmolar use; this is now "standard of care" in current radiography and angiography laboratories (4). Pharmacological prevention strategies have largely focused on intravascular volume expansion with Na-containing solutions. Various adjunctive therapies such as N-acetyl cysteine (NAC), fenoldopam, theophylline, and statins have been studied without any consistent beneficial therapeutic effect.

The precise mechanism by which volume expansion protects against CI-AKI is not known. It is speculative that volume may attenuate direct cellular damage from contrast, alter the hemodynamic profile in the renal vasculature, and affect the cell-signaling pathway to alter the neurohormonal response (5). The Na-containing fluids that have been studied include hypotonic saline (0.45% NaCl), isotonic saline (0.9% NaCl), and isotonic sodium bicarbonate. Prior to coronary angiography specifically, it appears isotonic saline is favorable compared to hypotonic saline in reducing the rate of CI-AKI (6). Unfortunately, there is no clear evidence to guide optimal fluid amount or duration. Most studies suggest fluids should be started at least 1 h prior to contrast administration and continued for three to 6 h post. Achieving a urine output of at least 150 mL/h within 6–12 h post contrast has been a benchmark in reduced rates of CI-AKI (6,7). Despite the recognition of intravascular volume depletion being a risk factor for CI-AKI, no randomized control trial had been conducted comparing

placebo to prophylactic volume expansion for the primary outcome of CI-AKI. Recently published in *The Lancet*, Nijssen and colleagues (8) present their primary results of no prophylactic volume expansion *vs.* volume expansion in high risk patients receiving contrast prior to cardiovascular or radiographical procedures (8,9).

The study was a prospective, randomized, open label, non-inferiority trial designed to assess the safety and efficacy of volume expansion on the prevention of CI-AKI (8). This was the first prospective randomized trial to compare prophylactic volume expansion to no pretreatment in high-risk patients. Aside from the intervention, baseline characteristics of both arms were similar and the identical formulation of contrast was used on each patient. However, subtle treatment differences may have occurred: for example, the time of day of exposure to contrast may have differed between the groups because of the delay required to infuse 0.9% NaCl to one group. Moreover, it is not clear whether the group assigned to no intravenous fluids was encouraged or prohibited from oral fluid ingestion or if the participants did it anyway because of the knowledge that the contrast can impair renal function. The primary outcome of incidence of CI-AKI was not statistically different between groups, and furthermore the study suggested increased cost-effectiveness with no prophylactic volume expansion in this patient cohort. This trial challenges the current kidney disease improving global outcomes (KDIGO) clinical practice guideline recommendations for prevention of CI-AKI. Nijssen and colleagues (8) must be recognized for the blinded randomization process, balanced baseline patient characteristics between arms, and challenging the standard of care. The trial was unique in that its setup was a non-inferiority design with a pre-defined non-inferiority margin of 2.1%, therefore to satisfy their hypothesis and meet the non-inferiority statistical significance the number of subjects enrolled was lower compared to a superiority trial (10). Importantly, this was a single center experience with a small sample size of approximately 600 patients. There were inherent assumptions made to set a non-inferiority margin of 2.1% given the paucity of prior randomized controlled trials. Therefore prior to changing practice standards, we must strive for large multi-centered randomized controlled clinical trials with realistic effect sizes (9).

Along with larger randomized trials, future directions should focus on standardized protocols for volume expansion based on objective measures such as inferior vena cava diameters, left ventricular end diastolic pressure, or even newer technology such as bioimpedance measurements. As McCullough and colleagues (9) have suggested, novel markers of kidney damage (NGAL, TIMP-2, IGFBP7) may detect CI-AKI earlier and without as much clinical heterogeneity. It also should be a priority to clarify if patients undergoing coronary angiography are at the same risk as patients undergoing other contrast procedures such as computed tomography or peripheral angiography. This relatively small single center study should not change practice guidelines. However, it can make the medical community reassess the diagnosis and treatment of CI-AKI and be the stepping stone for larger trials testing the similar hypotheses and challenging the current dogma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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