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EDITORIAL

Contrast-induced acute kidney injury in patients with acute necrotizing pancreatitis: Should it impact management of pancreatitis?

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Acute kidney injury (AKI) is a common and feared complication during critical illnesses, associated with short-term mortality and morbidity [1]. AKI is also associated with long-term consequences such as the development of chronic kidney disease and end-stage kidney disease [2].

Acute pancreatitis (AP) is a potentially life-threatening illness associated with systemic inflammatory response syndrome and the involvement of multiple organs, including the kidney. The prevalence of AKI was ~ 8% in a large national cohort of admitted patients with AP in the US [3]. AKI is more common in severe AP, with reported prevalence rates ranging from 15% to 70% [4, 5]. The presence of AKI worsens the outcome of severe AP [6]. Other risk factors for AKI in AP include sepsis, hypovolemia, exposure to nephrotoxic agents (radiocontrast, antibiotics, nonsteroidal anti-inflammatory drugs) and abdominal compartment syndrome.

Abdominal imaging with contrast-enhanced computed tomography (CECT) is crucial in managing severe AP. However, the risk of developing contrast-induced AKI (CI-AKI) [7] often comes in the way of its use. Therefore, CECT abdomen is often used restrictively in patients with severe AP [8], especially those with pre-existing kidney dysfunction.

It is important to answer the questions: whether the use of CECT leads to the development of AKI in patients with AP and has an impact on important clinical outcomes? Such a question can be best answered through a randomized clinical trial, in which patients with AP who have an indication for imaging are randomly allocated to receive CECT or an alternate imaging modality that does not involve an iodinated contrast agent.

This issue of the *Journal* reports the results of such a study. Gupta and colleagues [9] included patients with AP admitted to a single center who were identified to have necrotizing AP after a baseline CECT and deemed to require a follow-up CT scan at least one week later. Total 120 such participants were randomized — 60 each to receive CECT or non-contrast CT (NCCT). Patients could undergo one or multiple CT scans. The primary outcome was the development of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine definition. Secondary outcomes included length of hospitalization, need for intensive care unit (ICU) admission, length of ICU admission, need for dialysis, drainage of necrotic collections, surgery and mortality. The kidney function before imaging was normal in all participants. According to the intent to treat analysis, AKI developed in 45% of patients in the CECT arm vs. 31.7% in the NCCT arm, with a relative risk of AKI of 1.44 (95% confidence intervals 0.91–2.29, $p = 0.098$). ICU admission, length of ICU admission and pancreatic drainage requirement were more in the CECT arm than the NCCT arm. However, the lack of matching for baseline severity of AP is notable, with more patients in the CECT arm having severe AP (66.7% vs. 33.3%).

About 22% of 60 patients in the NCCT arm deviated from the protocol as they underwent CECT after the first NCCT. According to a per-protocol analysis, the relative risk of CI-AKI in the CECT group was 2.25 (95% CI 1.17–4.30, $p = 0.014$). However, the imbalance between the per-protocol groups was even greater, with the CECT group having more frequent severe AP and higher severity scores (including systemic inflammatory response syndrome [SIRS], Bedside index of severity in acute pancreatitis [BISAP] and Acute Physiology and Chronic Health Evaluation [APACHE-II]).

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The overall incidence of AKI and CI-AKI was 45% and 18.3%, respectively, in the CECT arm and the incidence of AKI was 31.7% in the NCCT arm. Compared to patients without AKI, patients with CI-AKI had poorer secondary outcomes such as mortality, need for ICU admission, length of ICU admission and need for drainage of pancreatic collection.

To overcome the challenges introduced by the lack of balance in the severity of AP between the groups, the authors performed a post-hoc sub-group analysis of the 43 patients with severe AP. In this sub-group, the occurrence of CI-AKI (21%) did not impact mortality, length of hospitalization or ICU admission. They also compared outcomes between CI-AKI and those who developed AKI unrelated to contrast agent use (AP-AKI). They found that the median duration of AKI was shorter (five days vs. 13 days) and the need for dialysis was lesser (1% vs. 16%) in the former. Other secondary outcomes such as mortality, need for ICU admission and length of ICU admission did not differ between patients with CI-AKI and those with AP-AKI. However, the paper does not mention the definition of recovery of AKI.

The results of this study suggest that CI-AKI was milder than other causes for AKI and did not impact mortality in patients with acute necrotizing pancreatitis, irrespective of the severity of AP. These findings align with studies in non-AP patients such as ICU patients [10, 11] and ischemic stroke patients [12], as discussed by the authors.

The limitations in this study drew our attention and we believe addressing these can aid in designing future clinical trials on this subject. The primary purpose of an RCT is to test the effectiveness of an intervention on an outcome(s) without a selection bias, while balancing confounding factors (known and unknown). The gross imbalance in the number of those with different severity of AP indicates a failure of randomization. It is important in this instance as patients with more severe AP are more likely to have AKI. In fact, some of the patients who were labeled as CI-AKI just because the rise in creatinine happened to correlate with the contrast administration temporally could have had AP-AKI, which throws into doubt the interpretation of data comparing CI-AKI and no AKI. This imbalance in severity perhaps also explains the greater need for drainage of collection in the CECT arm, as there is likely no causal association between CECT and drainage. A study restricting the enrolment of only patients with severe AP would remove this limitation, but would likely require multi-center collaboration. Another way to minimizing confounding variables could have been to stratify randomization based on the presence or absence of severe AP. Other methods to reduce confounding variables while designing the study are based on statistical tools such as variance minimization [13]. Furthermore, after the study is conducted, confounding variables are typically adjusted for by sub-group analysis, regression modeling and propensity scoring [14]. Although the authors performed a sub-group analysis of patients with severe AP, inferring from such a sub-group analysis comes at the cost of the lowered power and increased play of chance. Moreover, this sub-group hypothesis was not pre-specified, further limiting its value [15]. It is also unclear whether multiple AKI episodes were noted, as they are more likely to be associated with long-term CKD risk [16]. The authors did not provide data on other AKI risk factors such as diabetes mellitus, sepsis, hypovolemia or nephrotoxic drug use. No information is also provided about the pre-procedure protocol used to prevent AKI in those subject to CECT.

The next question is the choice of end-point in the study. The authors chose the development of AKI as the primary endpoint. What are the appropriate endpoints in such studies, i.e. what does it mean just to show AKI development after contrast administration? Does it impact outcomes? [17]. As CI-AKI may resolve over time without any consequences, evaluating a more clinically relevant endpoint that is meaningful to patients, like an intermediate or long-term consequence of kidney injury, is more practical and likely to inform clinical practice [17]. The largest trial to date looking at the prevention of CI-AKI after contrast exposure in high-risk patients, the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial [18], used primary outcome as a composite of death, dialysis requirement or a persistent serum creatinine increase of at least 50% from baseline, also termed "major adverse kidney events" at 90 days (MAKE90). The use of such outcomes has been common in the cardiology clinical trial landscape.

"Does CI-AKI in patients with severe AP impact the management of AP?" This question needs to be addressed in the broader context of the current understanding of CI-AKI. As it is, the evolution of practice standards with liberal use of iso-osmolar contrast agents and hydration with isotonic saline have contributed to dramatic reductions in CI-AKI incidence (Box 1). It has been said that the risks of CI-AKI are probably overstated, as initial studies were uncontrolled and relied on ICD codes with no adjudication to the cause. Several recent studies support this conclusion. Therefore, the diagnostic and therapeutic inertia (also called "renalism") that prevents patients, with or at risk of developing kidney disease, from receiving important, potentially life-saving interventions such as CECT for the evaluation of complications of AP needs to be abandoned.

Box 1 Good practices for prevention of contrast-induced - acute kidney injury in sick hospitalized patients [19, 20].

- Use iso-osmolar iodinated agents (e.g. iodixanol)
- Avoid repeated exposure to contrast agents < 72 h
- Identify risk factors — chronic kidney disease, acute kidney injury (AKI), diabetes mellitus, hypovolemia, congestive heart failure, cirrhosis, age > 70 years
- Avoid concomitant nephrotoxic agents, including analgesics, antibiotics and loop diuretics around contrast exposure, if clinically feasible, in at-risk individuals
- Intravenous hydration with isotonic saline (1 mL/kg/h 6–12 h pre-exposure and 6–12 h post-exposure) in patients with pre-existing kidney dysfunction (eGFR < 30 ml/min/1.73m^2 and not on dialysis) or ongoing AKI and other at-risk individuals (eGFR 30–44 ml/min/m^2 with other risk factors), taking care of volume overload
- Withhold metformin in at-risk individuals until 48 h after contrast exposure
- Monitor serum creatinine within 24-48 hours after contrast exposure

Declarations

Conflict of interest JB and VJ declare that they have no conflict of interest.

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