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Renal Safety Issues of Intravenous Iodinated Contrast Media Are Questionable

A Problemática da Nefrotoxicidade do Contraste Iodado Endovenoso É Questionável

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INTRODUCTION

In a recent letter to the editor, the author rightly highlighted the potential interference of contrast media (CM) used in imaging studies with clinical laboratory tests, proposing an algorithm to manage these interactions.[1] We commend the author for this effort, but we believe it is crucial to address the underlying assumptions regarding the safety of intravenous contrast media, particularly its association with nephrotoxicity. Nephrotoxicity from intravenous iodine-based media remains a debated issue, with diverging views in the literature. We aim to expand on those concerns and hereby present a brief review of the current evidence on contrast-associated acute kidney injury (CA-AKI), or post-contrast acute kidney injury (PC-AKI), as well as our view of the evolving guidelines regarding its use in patients with kidney injury.

Contrast nephrotoxicity: a debatable topic

The aforementioned letter cites the European Society of Urogenital Radiology (ESUR) guidelines, which highlight potential safety issues with contrast media use, specifically mentioning the term 'nephrotoxicity'.[2] However, these guidelines, while alluding to "potential safety issues", do not offer explicit evidence on that matter. The safety of intravenous contrast regarding nephrotoxicity has been a topic of debate for decades, with more recent studies suggesting that the risk is often overstated.[3]

The term 'contrast-induced nephropathy' emerged in the 1950s, when renal failure was observed in some patients following intravenous injection of high-osmolar contrasts. Since then, modern low-osmolar iodine contrast agents have been developed to reduce nephrotoxicity. In fact, the definition of 'contrast-induced nephropathy' was redefined in 2019 to the less causally charged 'contrast-associated' AKI and then to 'post-contrast' AKI, highlighting the evolution in our understanding over the years.[4]

Post-contrast acute kidney injury: what is the evidence?

While the early studies lacked adequate control groups, making it difficult to establish a causal link, several recent observational studies and meta-analyses have been challenging the long-held belief that the low-osmolar iodinated contrast agents significantly increase the risk of AKI. For example, a recent meta-analysis found that intravenous contrast use was not significantly associated with an increased risk of AKI when compared to non-contrast computed tomography (CT) scans.[5] Specifically, the odds ratio for developing AKI was found to be 0.94 (95% CI: 0.83 to 1.07), suggesting that contrast-enhanced CT scans do not pose a significant risk in the majority of patients. Those studies are limited by the challenges of making causal assumptions in observational research due to their non-experimental nature, and randomized controlled trials (RCTs) have not yet been conducted because of ethical concerns. However, a recent quasi-experimental observational study found no association between intravenous contrast and long-term kidney injury.[6] This study used a regression discontinuity design to attenuate selection bias, which has remained the most problematic issue in observational studies on contrast media and kidney injury. This observational method reduces selection bias by establishing a threshold for the use of a given intervention (e.g., D-dimer levels in suspected pulmonary embolism as a guide for ordering angiographic chest CT) that does not depend on the typical confounding variables (e.g., age, GFR, and diabetes status, which are unrelated to the chosen threshold). Naturally, this study has limitations, namely the fact that the median eGFR was 80 mL/min/1.73 m^2 and they used an eGFR threshold of 45 mL/min/1.73 m^2 rather than lower values, thereby limiting the generalizability of

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their findings to high-risk patients.

More recently, a retrospective study analyzed approximately 15 000 patients with AKI at admission who had undergone intravenous contrast administration and found no association with persistent AKI or dialysis initiation, utilizing propensity-weighted and entropy-balanced statistical techniques in order to reduce selection bias and imbalances in measured covariates.[7] Dialysis initiation is likely the most concerning outcome of AKI after mortality, and this study supports the notion of renal safety with intravenous contrast. This study, like the others mentioned, is observational in nature and therefore limited by its lower level of evidence. However, considering the entire body of literature, the evidence from the studies with higher quality does not seem to indicate an association between intravenous contrast and AKI. Therefore, the burden of proof seems to be on the claim that such association is (still) real and clinically significant.

Ultimately, well-conducted, large and multicenter RCTs would be the ideal method to achieve proper group balance and avoid selection bias, but it remains uncertain whether such studies will ever be conducted.

Intra-arterial *versus* intravenous contrast: key differences

One important distinction to be made, often overlooked in discussions of contrast nephrotoxicity, is the difference between intravenous and intraarterial iodinated contrast administration.[8] While intraarterial iodinated contrast, commonly used in angiographic procedures, may pose a risk for renal injury, this risk is confounded by the invasiveness of the procedures themselves. For instance, vascular manipulation during an angiogram can induce renal ischemia, making it difficult to determine whether any resulting kidney injury is due to the contrast agent, the procedure, or a combination of both. Therefore, intraarterial CA-AKI is an even more difficult topic and we argue it should be studied and discussed separately from intravenous CA-AKI. For clarity, it is worth noting that some angiographic procedures, such as pulmonary angiography, are performed using venous puncture with intravenous iodinated contrast. The risks of contrast in these procedures are consistent with those discussed for intravenous iodinated contrast administration in general, as the route of administration does not differ in these cases.

Intravenous contrast in clinical practice: evolving guidelines

The current guidelines on contrast media use reflect this evolving understanding. The ESUR guidelines, as well as those from other major radiological and nephrology societies, have progressively relaxed their recommendations regarding the use of intravenous contrast in patients with chronic kidney disease (CKD). Notably, the 2020 consensus from the American College of Radiology and the National Kidney Foundation suggests that intravenous contrast should not be withheld from patients with an eGFR greater than 30 mL/min/1.73 m^2, a significant departure from earlier and more restrictive guidelines.[9] However, just as we have seen changes in the definition of CA- and PC-AKI over the years, we can imagine that this threshold may also be modified in the future based on the latest evidence. The significant clinical utility of angiographic CT in diagnosing potentially life-threatening conditions, especially in the acute context, cannot be overlooked.

Intravenous contrast in clinical practice: future algorithms, evidence, and guidelines

Clinical algorithms are designed to guide clinicians in practice. When it comes to intravenous contrast administration, it is essential to align its use with clinical patient data. While these tools can be beneficial, it is important to acknowledge the ongoing uncertainty surrounding contrast-associated renal safety. Such algorithms can support decision-making but should be applied with an understanding of the limitations in the available evidence, especially as the assumption that contrast media pose a significant risk of nephrotoxicity, even in patients with CKD, is increasingly being questioned.

A recent Canadian guideline, supported by the Canadian Association of Radiologists and developed by a multidisciplinary group including radiologists and nephrologists, states that the causality between contrast and kidney injury remains unproven. It recommends that even when eGFR ≤ 30 mL/min/1.73 m^2, the risks of CA-AKI should be balanced against the risks of delayed and suboptimal imaging.[10]

This research field would benefit from more comprehensive studies, ideally RCTs, to provide definitive answers on the long-term renal safety of contrast-enhanced imaging studies. In the meantime, clinicians must continue to balance the benefits of contrast-enhanced imaging against the potential risks, particularly in high-risk patients, with the notion that, as of late 2024, the burden of proof lays on those claiming that AKI is associated with intravenous contrast.

CONCLUSION

The nephrotoxicity of contrast media, particularly intravenous iodinated contrast, remains a topic of debate in the

medical community. While older guidelines and clinical practices have tended to err on the side of caution, particularly in patients with CKD, recent evidence suggests that the risks associated with intravenous contrast may have been overestimated and, in present times, may even not be real. For most patients, including those with mild to moderate CKD, the benefits of contrast-enhanced imaging likely outweigh the risks. Ultimately, more research is needed, particularly in patients with AKI and eGFR below 30 mL/min/1.73 m^2, to definitively determine the safety of repeated contrast exposures.

AUTHOR CONTRIBUTIONS

BVP, MB: Study conception and design, literature search, writing and critical review of the manuscript.

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