REVIEW

Renal Risk of Contrast-Enhanced Imaging – Is It a Myth? The Latest Opinions of the Guidelines

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Abstract

Over the last decade, several divergent views have been expressed regarding the effect that iodinated contrast agents may have on renal function. Evidence-based medicine often requires the recommendation of high-performance contrast-enhanced imaging exams for precise positive diagnosis. The fear of intravenous contrast use in patients with elevated serum creatinine seems to become an old dogma, outdated by the benefits of the procedures. Patients with glomerular filtration rate below 30 mL/min/1.73 m² can be protected by peri-procedural hydration and withdrawal of other nephrotoxics. Whatever the degree of risk, current guidelines recommend contrast-enhanced investigations in any situations where the advantages for the diagnosis are certain.

Keywords: contrast agent, nephrotoxic, contrast-induced AKI, risk, prophylaxis, hydration.

Rezumat

În ultimii ani au fost avansate numeroase opinii divergente cu privire la efectul nefrototoxic al substanțelor de contrast. Medicina bazată pe dovezi impune frecvent prescrierea de investigații imagistice performante, punându-ne în fața unei dileme: este justificată teama de prescriere a mediilor de contrast la pacientul renal cronic, sau continuăm să perpetuăm o dogmă veche fără fundament științific solid? Studiile recente pe care se bazează recomandările ghidurilor moderne arată că nefropatia de contrast este o excepție la valori ale ratei filtrării glomerulare de peste 30 ml/min/1,73 m², iar sub acest nivel poate fi prevenită cu hidratare corectă peri-procedurală și retragerea altor nefrotoxice. Un raport pozitiv beneficii/riscuri este cheia deciziei medicale în fiecare situație care impune investigație cu contrast.

Cuvinte cheie: substanță de contrast, nefropatie de contrast, risc, profilaxie, hidratare.

Over the last decade, several divergent views have been expressed regarding the effect that iodinated contrast agents may have on renal function. From the classic contraindication of intravenous contrast use in patients with elevated serum creatinine, to the more nuanced indication of proper hydration and after-investigation monitoring of the renal patient to whom we decide to administer a contrast media, in the recent years it has

been reached to the denial of the nephrotoxic risk of these investigations.

A precise positive diagnosis is crucial in our days, and this often requires the prescription of high-performance imaging. On the other hand, the modern evidence-based medicine penalizes us when it detects iatrogenic adverse events, complications which could have been avoided by better medical decisions. There-

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fore, is it the risk of acute kidney injury enough to justify the fear for prescribing imaging investigations, or is time to reconsider the old dogma? In order to decide where we stand at the moment and what attitude to follow in our current practice, it is imperative to study the most recent opinions of the guidelines and the results of the latest studies on the subject of renal injuries due to contrast media.

It has been documented that iodinated contrast agents administered intravenously can act in the renal tubules by direct cell toxicity and by the release of vasoactive mediators, inducing medullary vasoconstriction that causes hypoxia in tubular cells¹⁻⁴. Several studies conclude that they are also involved in cytotoxicity with the consequences of an imbalance in the local level of vasodilators, activation of oxidative stress, increased viscosity in the peritubular capillaries and functional deficit of mitochondria in the tubular cells⁵⁻⁷.

Due to these tubular processes, contrast-induced acute kidney injury (AKI) develops, diagnosed as an increase in serum creatinine of more than 0.5 mg / dl or more than 25% of baseline within 2-5 days after administration of the contrast media⁸⁻¹⁰.

There are specialists that consider the contrast-induced AKI (CI-AKI) as a serious condition, one of the most common cause of AKI and an important cause of in-hospital morbidity and mortality, underlying its potential to develop nonreversible renal damage and chronic kidney disease¹¹⁻¹⁴. In consensus with these opinions, the KDIGO (*Kidney Disease Improving Global Outcomes*) 2012 guidelines rely on studies performed in that period and concludes that contrast-induced AKI incidence is extremely variable but it can reach 25% of the investigated patients in some facilities; therefore, for safety, it recommends prophylactic actions in all patients with glomerular filtration rate (GFR) below 60 mL/min/1.73m² to whom we intend to administer intravascular contrast (intravenous or intra-arterial)^{8,15}. The *European Society of Urogenital Radiology*, based on studies by Choyke and colleagues, indicates to assess the risk of CI-AKI by determining the presence of proteinuria, an investigation that is easier to perform than creatinine and GFR calculation, requiring only urinary strips screening; the guide indicates pre- and post- contrast hydration prophylaxis and serum creatinine monitoring at 2-5 days after contrast only in patients with detected proteinuria, considered to have pre-existing renal impairment^{10,16}.

Classic cardiology guidelines contain warnings of the risk that coronary angiography poses to the patient with any kind of renal function impairment, even thou-

gh that modification is not clinically manifest; a percentage of 5-10% is stated for patients who may develop CI-AKI after intravascular injected contrast during the procedure^{17,18}. Prophylaxis actions are indicated in all patients with GFR below 60 mL/min/1.73m², namely the use of low contrast doses, low-osmolality agents, the avoidance of other nephrotoxic drugs and ensuring an appropriate hydration during the procedure^{17,18}.

The last five years bring a change of opinion. Unlike the recommendations of classical guidelines, the latest statement from the *American Society of Radiology* is based on the results of recent clinical trials and considers that the effect of iodinated contrast media on renal tubules has been overestimated¹⁹. In support of this assertion, the experts point out the differences stated by KDIGO between 'contrast-associated AKI' (CA-AKI) and 'contrast-induced AKI' (CI-AKI), meaning that different kind of subsequent causes of AKI were blamed on the contrast media^{8,19}. We should diagnose CI-AKI only when a direct causality relation can be established between the contrast administration and the renal damage. This separates the situations in which AKI develops in patients with multiple renal risk factors and who have undergone an imaging investigation in the last week, versus patients who develop AKI immediately after performing the contrast imaging and in whom the causal relationship between the two is certain. According to this guideline, CI-AKI is a rare entity, being highlighted in very few cases of renal insufficiency developed after an imaging investigation/procedure. The combination of other nephrotoxic drugs and dehydration are factors that far exceed the risk potential of iodinated contrast media. For these reasons, pre-contrast hydration and withdrawal of nephrotoxic medication would almost completely cover the risk of contrast media nephrotoxicity. Therefore, the guideline imposes these two precise actions only for patients with GFR value situated below 30 mL/min/1.73 m², considering that above this rate of glomerular filtration there is no risk for the performance of contrast imaging¹⁹.

Consistent with this new perspective, the Medscape platform states in February 2020 that pre-contrast hydration would no longer be considered necessary before contrast enhanced computed tomography examination in renal patients with GFR over 30 mL/min/1.73m²²⁰. This time, the claim is based on the results of a recent Dutch study, Kompas, which demonstrated the same creatinine values 2-5 days after iv contrast administration in patients with chronic kidney disease (CKD) stage 3 (GFR 30-60 mL/min/1.73 m²) included in the

Table 1. CI-AKI prophylaxis methods and pros / cons studies¹¹

Prophylaxis strategies	„Pros“ studies	„Cons“ studies
Hydration with 0.9% saline 1 ml/kg/h, 4-6 h pre and post	Mueller 2002 ²⁷ , Trivedi 2003 ²⁸ , Brar 2014 ²⁹ , Luo 2014 ³⁰	Timal 2020 ²¹ , Nijssen 2019 ²²
Sodium Bicarbonate alone or added in 0.9 % saline solution	Van der Molen 2018 ²⁴ , Merten 2004 ³¹ , Hoste 2010 ³²	Brar 2008 ³³ , Solomon 2015 ³⁴
N-acetylcysteine 600 mg bid	KDOGO 2012 ⁸ , Lameire 2006 ³⁵	ACT investigators 2011 ³⁶ , Zagler 2006 ³⁷
Prophylactic hemodialysis	-	Ozkok 2017 ¹¹ , Cruz 2012 ³⁸
Stop nephrotoxic medication ACEI/ARB, metformin	Rim 2012 ³⁹ , Thomsen 1999 ⁴⁰	Rosenstock 2008 ⁴¹ , Owen 2014 ⁴²

trial²¹. The same conclusion results from investigations in the AMACING study performed by Maastricht University Medical Centre and published in 2017²².

Therefore, current opinion, accepted by all guidelines, is to apply pre-procedural prophylactic measures only to stage 4 or 5 CKD patients programmed to receive intra-vascular contrast media. These measures, available in any medical facility, include: the use of substances with the lowest possible osmolality; isotonic saline hydration before and after contrast (use of sodium bicarbonate only in the presence of metabolic acidosis), with caution in heart failure cases; withdrawal / avoidance of other nephrotoxics on the day/around of investigation (eg. angiotensin converting enzyme inhibitors, metformin, nonsteroidal anti-inflammatory drugs, aminoglycosides); avoidance of early repetition of contrast administration. Other prophylaxis methods have not proven effective, although several of them are still used in daily practice (Table 1)^{11,23,24}.

The prognosis is good in the majority of cases, with renal function normalizing in 1-3 weeks^{17,26,43}. Prophylactic hemodialysis has no benefits in CI-AKI; in confirmed AKI, initiating of dialysis follows the same indications as in other types of AKI, with the peculiarity

of substantial benefit in early initiation in patients with clinically manifest hyperhydration.^{8,25,44}

CONCLUSIONS

Acute renal injury is a severe condition with significant lethal potential, but its occurrence due to the administration of iodinated contrast agents is an exception in patients without renal impairment and is minimal in early chronic kidney disease. Patients with glomerular filtration rate below 30 mL/min/1.73 m² can be protected by pre-contrast hydration and withdrawal of other nephrotoxics. Whatever the degree of risk, current guidelines recommend the administration of contrast in any situations where the benefits for the diagnosis or for the treatment are certain.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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