Intravenous Contrast Agents: Risk of Renal Complications

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Abstract

The need for intravenous contrast-enhanced imaging, either in the acute or outpatient setting, is steadily increasing over the last years. A common concern for both clinicians and radiologists is the probability of the associated renal complications. In this review we present contemporary data on the safety and risk of development of acute kidney injury (AKI) after the administration of iodinated contrast agents and the development of nephrogenic systemic fibrosis (NSF) after gadolinium-based contrast media exposure (GBCM). Although the risk of AKI after iodinated contrast enhanced imaging is higher in patients with established chronic kidney disease and decreased kidney function, the direct link between these agents and induced AKI is missing as there are no well designed randomized controlled trials to support causal relationship. However, in patients with an estimated glomerular filtration rate of less than 30 ml/min/1.73m^2, prophylaxis should be applied with intravenous hydration with normal saline before performing the exam and cessation of metformin and other possible nephrotoxic drugs. Concerning GBCM exposure and NSF, current data and guidelines support that the risk for NSF development is minimal (if any) with modern GBCMs even in patients with end stage kidney disease.

Key words: *Contrast associated AKI; contrast induced AKI; nephrogenic systemic fibrosis*

INTRODUCTION

One of the most debilitating adverse effects reported after intravenous radiocontrast administration is acute kidney injury (AKI) of various stages and severity (Table 1) [1]. However, several recent observational but not randomized control studies have shown that such an association between contrast administration and AKI does not exist in the current era of modern agents and doses [2]. This notion though has several potential biases based on the baseline characteristics of patients involved, mainly concerning differences on the risk for AKI or even the appropriately timed repeat creatinine measurements. In any case, and despite several studies showing no evidence of connection between radiocontrast administration and AKI, many clinicians may still express concern over contrast exposure in patients with reduced kidney function or even avoid diagnostic imaging due to fear of AKI especially in the acute setting [3]. Thus, in this review we will examine the evidence from the most important studies on the risk of renal complications after the administration of intravenous contrast agents.

Contrast-associated acute kidney injury (CA-AKI) and contrast-induced acute kidney injury

An AKI that occurs within 48 hours of contrast administration is referred to as contrast-associated (CA-AKI). Whereas an AKI that can be causally linked to contrast

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Table 1. *AKI stages according to baseline serum creatinine values and urine output.*

Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline or ≥ 0.3 mg/dl increase	< 0.5 ml/kg/h for 6-12 hours
2	2-2.9 times baseline	< 0.5 ml/kg/h for ≥ 6-12 hours
3	3 times baseline or increase in serum creatinine ≥ 4 mg/dl or initiation of renal replacement therapy	< 0.3 ml/kg/h for ≥ 24 hours or anuria for ≥ 12 hours

administration is referred to as contrast-induced acute kidney injury (CI-AKI). CI-AKI is a subset of CA-AKI and suggests a causal relationship between intravenous contrast administration and the development of AKI. Only studies with a well-matched control group can demonstrate a possible causal relationship of iodinated contrast administration with the development of acute kidney injury [4]. While there is much evidence for the existence of CA-AKI, studies related to CI-AKI are only few.

Presumed pathogenesis of contrast induced AKI

Following intravascular administration, iodinated contrast agents cause immediate and short-term renal vasodilation which is very soon followed by vasoconstriction [5]. In some animal models, the intravascular administration of iodinated contrast results in decreased renal blood flow and a reduction in the partial pressure of oxygen of the outer renal medulla [6]. This adverse hemodynamic effect of contrast is also observed in studies of healthy human subjects [7]. Moreover, iodine contrast drugs can induce osmotic diuresis which in turn promote tubular flow, O2 consumption and enhance tubular epithelial cell injury [8].

contrast-associated AKI

The risk of CA-AKI (AKI of any etiology after iodinated contrast administration) increases with each increase in chronic kidney disease (CKD) stage. Using the KDIGO stage I based on serum creatinine criteria, the risk of CA-AKI is approximately 5% greater for estimated glomerular filtration rate (eGFR) of 60– 90 mL/min/1.73 m^2, 10% for eGFR 45–59 mL/ min/1.73 m^2, 15% for eGFR 30–44 mL/ min/1.73 m^2, and 30% for eGFR less than 30 mL/min/1.73 m^2 [9]. This risk is much higher than the risk of CI-AKI because it includes any AKI that coincides with contrast media administration [4]. Multiple patient-related risk factors have been associated with CA-AKI. The primary risk factor is low eGFR. Some studies find diabetes mellitus to be an additional risk of CA-AKI. Additional risk factors include administration of nephrotoxic agents, hypotension and hypovolemia, albuminuria, and reduced renal perfusion (e.g., congestive heart failure) [10].

Effect of contrast medium osmolality

The initial contrast media used in clinical practice were 'high osmolal' with osmolalities much greater than blood (i.e., 1500–2000 mOsm/kg). Following the introduction of 'low-osmolal' contrast media (osmolality ~ 600–850 mOsm/kg), clinical trials and meta-analyses demonstrated lower risk for CA-AKI with these agents compared with 'high-osmolal' media [11]. Despite their name, low-osmotic contrast media (LOCM) are hyperosmotic (approximately 600 mOsm/kg) relative to both isoosmotic (IOCM) (approximately 290 mOsm/kg) and blood (approximately 290 mOsm/kg). Nevertheless, the chemical structure of IOCMs makes them more viscous than LOCMs and most currently used iodinated contrast media are classified as LOCMs. There are no clinically confirmed differences in the risk of CA-AKI between LOCM and IOCM contrast media. Indirect evidence suggests that iohexol, which is a LOCM, may have a higher risk compared with other LOCMs, but this potential risk difference has not been confirmed [12].

Contrast Induced AKI

In general, the risk of CI-AKI is lower than the risk of CA-AKI, but the risk in those with established severe kidney disease (either high grade CKD or AKI) is not known. Some observational studies have shown no evidence of CI-AKI, irrespective of CKD stage, while others have found evidence of CI-AKI only in patients with severely reduced kidney function [13, 14]. In such studies, the risk of CI-AKI has been estimated to be almost 0% for eGFR greater than or equal to 45, 0%–2% for eGFR 30–44, and 0%– 17% for eGFR less than 30 mL/min/1.73 m^2 [14].

In a study of 12,508 patients the incidence of AKI increased significantly with decreasing baseline eGFR. However, this incidence was not significantly different between the contrast-enhanced and non-contrast-enhanced groups for any eGFR subgroup [9]. Further-

more, a meta-analysis by McDonald and colleagues that included 13 studies with a total of 25,950 patients demonstrated that the risk of AKI following procedures with intravascular contrast administration was similar to the risk following procedures that did not utilize contrast [15]. In a study of 611 patients in total, with a median age of 65 years and a serum creatinine level on the day of computed tomography of 1.13 mg/dl for the non-contrast group and 0.87mg/dl for the contrast-enhanced group, the adjusted odds ratio for developing AKI for the patients who received intravenous contrast media (ICM) was 1.03 (95% CI 0.64–1.66, p=0.90). No significant association was found between ICM and increased plasma creatinine at long-term follow-up [16]. Another cohort study included all emergency department patients aged 18 years and older who underwent a D-dimer test. There was no association of iodinated contrast media administration with eGFR up to 6 months later. Similarly, there was no evidence of an association with the need for renal replacement therapy and the occurrence of AKI. Subgroup analyses showed a possibly higher risk among patients with diabetes [17]. Thus, although no randomized controlled trial has been conducted, evidence suggests that ICMs contribute little, if any, to the occurrence of AKI [18].

Prophylaxis

Overall, patients with CKD stage 4 or 5 have a relative, but not absolute, contraindication to receive iodinated contrast media. If contrast media is required for a life-threatening diagnosis, it should not be withheld based on kidney function. If a decision is made to administer iodinated contrast media, then prophylactic normal saline administration is indicated if there are no contraindications [4]. Due to the lack of proven benefits, risks, and costs, acute dialysis should not be performed or the dialysis schedule changed solely on the basis of iodinated contrast media administration, regardless of residual renal function [4]. Prophylaxis is indicated for patients who have AKI or an eGFR less than 30 mL/min/1.73 m^2 and are not on chronic dialysis. The risks of prophylaxis, especially in hypervolemic patients or those with congestive heart failure should be considered before initiating prophylactic normal saline administration. Prophylaxis is not indicated for the general population or patients with a stable eGFR ≥ 30 mL/min/1.73 m^2 [4].

If an iodinated contrast imaging procedure is urgently indicated and there is insufficient time for prophylaxis, then post-examination prophylaxis can be considered. For prophylaxis, hydration with isotonic saline (0.9% N/S) is the preferred method as other agents such as acetylcysteine or sodium bicarbonate have shown no benefit [19]. Typical N/S 0.9% regimens are initiated 1 hour before and continued 3-12 hours after contrast administration, with doses ranging from fixed (e.g., 500 mL before and after) to weight-based volumes (1-3 mL/kg per hour) but ideal volume or rates of administration are not established. Longer regimens (approximately 12 hours) have been shown to reduce the risk of CA-AKI compared with shorter regimens. Oral hydration has not been well studied [10]. In patients with AKI or eGFR ≤ 30 mL/min/1.73 m^2, potentially nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, antibiotics (aminoglycosides and amphotericin) and chemotherapeutics (platinum) may need to be discontinued for 24 to 48 hours before and 48 hours after exposure [20]. Metformin is another agent that is appropriate to stop before contrast enhanced CT and discontinuation should be maintained for at least 48 hours in this group of patients [21]. It is unknown whether renin-angiotensin-aldosterone system (RAASi) inhibitors should be maintained. Given the lack of strong evidence that continued RAASi is beneficial, consideration should be given to discontinuing RAASi in patients at risk for at least 48 hours before elective contrast-enhanced CT for preventing hyperkalemia and hypotension should AKI develop [21].

Correlation between administration of gadolinium-based contrast media (GBCM) and nephrological complications

The frequency of magnetic resonance imaging (MRI) examinations with the administration of a paramagnetic contrast media has increased significantly in the last decade and is predicted to increase further [22]. In the United States, GBCMs are used in 30% to 45% of the approximately 40 million MRI procedures performed each year [23]. As more patients undergoing these tests are older and suffer from multiple comorbidities, including acute or chronic kidney dysfunction, it is imperative to investigate the possibility of additional burden on kidney function from the administration of the paramagnetic substance or the occurrence of another related nephrological complication. Clarifying the presence of such complications is of particular importance as it is not uncommon to delay or even refuse to perform tests with the administration of a paramagnetic substance in cases of patients with pre-existing chronic kidney

disease and reduced glomerular filtration rate [24].

Gadolinium has been used in most intravenous MRI contrast agents because it is highly paramagnetic, allowing the distinction between normal and abnormal tissues in humans. However, "free" gadolinium exhibits multiple toxicities (mainly cytotoxicity) due to its insolubility [5]. In order to minimize toxicity, gadolinium is chelated to organic ligands, which confer more favorable pharmacological and toxicological properties. Most GBCMs are distributed primarily in the extracellular fluid, exhibit little protein binding, and are excreted primarily in the urine via glomerular filtration. Finally, GBCMs are classified as linear or macrocyclic, based on the molecular structure of the organic ligand, and as nonionic or ionic, based on their net charge in solution (Table 2) [25].

Gadolinium and nephrotoxicity

Gadolinium-based contrast media (GBCM) are in general considered non-nephrotoxic. Nevertheless, at doses considerably higher than the approved dose, GBCM may be nephrotoxic as demonstrated in patients and in experimental settings [26, 27]. Very high doses of GBCM have been associated with cases of AKI, but there are no controlled clinical studies demonstrating a clinically significant nephrotoxic risk at on-label doses [26, 28]. Thus, clinicians should consider that on-label dosing of intravenous group II or group III GBCM does not increase the risk of AKI, and no special precautions are indicated for kidney function safety (Table 2). In general, only the approved GBCM dose (0.1 mmol/kg) should be administered during a single imaging session [29]. Moreover, there are no indications that patients receiving other nephrotoxic agents are at increased risk for AKI after an MRI with GBCM administration and such examinations can be performed as scheduled. Finally, MRIs with GBCMs can be performed irrespective of the timing of additional iodinated contrast CTs without increased risk for AKI [30].

Nephrogenic systemic fibrosis (NSF) and GBCM Exposure

NSF is a potentially fatal systemic fibrotic condition that occurs almost exclusively in patients with AKI or severe CKD (eGFR < 30 mL/min/1.73 m^2). Skin and subcutaneous abnormalities (e.g., skin thickening, pruritus, hyperpigmentation), as well as ocular findings (sclerotic plaques) are common, but NSF can also cause visceral fibrosis (e.g., lung, esophagus, and heart) [31]. NSF is characterized by signs of cutaneous edema and erythema in the extremities that may sometimes progress to thickened, woody, and contracted skin. The condition has been associated with the use of linear GBCMs in patients with advanced CKD and rarely develops (if at all) after the use of macrocyclic GBCMs. In recent years, the incidence of NSF has decreased or disappeared [29].

The link between GBCM and NSF was first identified in 2006 and has since been confirmed in numerous studies [32, 33]. Patients at greatest risk for NSF include those on renal replacement therapy, those with AKI, and those in stages 4 or 5 CKD with exposure to group I GBCMs, especially if repeated doses of group I GBCMs are administered or at higher than recommended doses [30].

The risk of developing NSF differs between the different groups of GBCM (Table 2). Most NSF cases have been associated with Group I GBCMs, however, this

Table 2. *Classification of GBCMs related to association with Nephrogenic Systemic Fibrosis.*

Substance	Structure	American College of Radiology Group
Gadodiamide	Linearnonionic	I
Gadoversetamide	Linearnonionic	I
Gadopentetatedimeglumine	Linearionic	I
Gadobenatedimeglumine	Linearionic	II
Gadoteridol	Macrocyclic non ionic	II
Gadobutrol	Macrocyclic non ionic	II
Gadoterateme glumine	Macrocyclic ionic	II
Gadoterateme glumine	Macrocyclic ionic	II
Gadoxetatedi sodium	Linear ionic	III

group of contrast media is by now mostly not used at all. For Group II, only a few (if any) cases of NSF have been reported [34] and for Group III GBCMs again only a few (if any) cases have been reported [35]. In a recent meta-analysis of 16 studies, including 4931 patients with CKD stage 4 or 5 who were given a Group II GBCM and followed for up to 72 months, no NSF was reported [34]. In a meta-analysis of observational studies, all patients with NSF were reported to have renal dysfunction with a higher risk of NSF for GFR < 15 ml/min (i.e., stage 5 CKD). Eighty percent (296 of 370) of patients with NSF were on dialysis, suggesting that this is an important risk factor. For 57 patients with NSF who were probably not on dialysis, GFR was reported to range from 0 to 40 ml/min, with a mean of 15 ml/min, but most importantly, the majority of these patients (88%) had received a higher than standard dose and in some cases GBCMs were administered intra-arterially [36]. In general, only the approved dose of GBCM should be administered but the use of a lower dose for NSF prevention is not supported and may compromise image quality [34].

Excretion of GBCAs is dependent on kidney function and in patients with normal GFR, GBCMs half-life is approximately 1.5 hours, with the majority excreted within 24 hours. Thus, in patients with established CKD or AKI, the half-life of GBCMs is prolonged according to CKD or AKI stage with a span of more than 24 hours in severely diminished GFR [37, 38]. Accordingly, hemodialysis removes sufficiently GBCAs with ~70% clearance after 1 session [30], but such intervention offers no proven reduction in the risk of NSF development [39]. Furthermore, in patients with end stage kidney disease on maintenance hemodialysis, GBCMs should better be administered before a scheduled dialysis session but otherwise sessions should be performed on the regularly scheduled basis [29]. Overall, the risk of NSF is extremely low for group II GBCMs even in patients with diminished kidney function and based on these data, many societies have issued recommendations to liberalize the administration of group II GBCMs [40, 41].

CONCLUSION

Modern iodinated contrast agents [LOCM, IOSC) are minimally nephrotoxic in patients with eGFR > 30 ml/min/1.73m^2. However, in patients with compromised renal function (AKI or eGFR < 30 ml/min/1.73m^2), measures should be taken to reduce potential nephrotoxicity, including intravenous hydration with 0.9% N/S and discontinuation of nephrotoxic agents. Well-designed prospective RCTs in patients with similar clinical characteristics and morbidities are necessary to clarify the type and degree of potential nephrotoxicity of iodinated contrast agents, especially in patients with impaired kidney function. Modern paramagnetic contrast agents at the recommended dose are not nephrotoxic and are rarely (if at all) associated with the occurrence of NSF.

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