REVIEW ARTICLE

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Contrast agents in Nephrology – a literature review

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ABSTRACT

Contrast agents are widely used in ambulatory and hospitalized patients, as a complement to imaging studies, improving diagnostic accuracy. Patients with chronic kidney disease are at increased risk for adverse events related to contrast administration. In this review, we will summarize the current evidence on this topic.

Keywords: Radiocontrast, gadolinium, contrast-induced nephropathy, nephrogenic systemic fibrosis

INTRODUCTION

According to data from the *Portuguese Registry of Dialysis and Transplantation 2018*, the number of patients with chronic kidney disease (CKD) stage 5d or 5t was 20,730, meaning that the prevalence of patients on dialysis in Portugal is over 1.264 per million population[1]. We can conclude that the prevalence of CKD stage 3 to 5 is higher, given that the majority of CKD patients never reach dialysis. Nevertheless, a study published in 2011 revealed that, in 2008, the prevalence of CKD in Portugal was 6.1%[2].

As others, CKD patients are often subjected to radiological examinations, some of which require contrast media, such as coronary angiography (since cardiovascular pathology is almost universally present in patients with CKD[3]), contrast-enhanced computer tomography (CT), magnetic resonance imaging (MRI) or even arteriovenous fistula angioplasty.

Although the risk of renal function deterioration associated with contrast administration is low in the general population[4], it may be as high as 25% in patients with pre-existing renal impairment or with certain risk factors[5,6]. Moreover, the risk for complications associated with the use of contrast in MRI exams is also increased in patients with renal disease.

In this review, we aim to summarize risk factors that predispose to renal injury after exposure to contrast media, and the main preventive strategies studied so far. We will focus on contrast-enhanced CT and MRI enhanced with gadolinium-based contrasts.

CONTRAST-ENHANCED CT AND CONTRAST-INDUCED NEPHROPATHY

Contrast-induced nephropathy (CIN) is defined as an absolute or relative increase in serum creatinine that occurs after exposure to a contrast agent when other causes of renal impairment are excluded[7]. It is the third leading cause of acute kidney injury (AKI) in hospitalized patients, accounting for 11% of the cases[8] and is associated with increased risk of mortality, cardiovascular events, renal failure, and prolonged hospitalization[9]. It has known risk factors and preventive strategies, as we will see.

High osmolality vs. low osmolality and iso-osmolality contrast media

Radiocontrast agents can be ionic or non-ionic and those are classified according to their osmolality. The early reports of contrast-induced nephropathy happened with ionic and high osmolality contrast media, which were proven to have a 3.3 times greater risk of causing nephropathy when compared to low osmolality contrast media[10]. Thus, hyperosmolal contrasts are not currently used. Nowadays, radiologists use ionic and non-ionic low-osmolal agents, which have higher osmolality than plasma, as well as non-ionic iso-osmolal agents, with a similar osmolality to plasma[11].

It seems that the risk of developing CIN is allied to the osmolality and not to the charge by itself. Only one study compared ionic agents according to their osmolality, and the low-osmolal agents revealed to be less nephrotoxic than the hyperosmolal agents[12]. Most studies compared non-ionic low-osmolal agents with ionic hyperosmolal contrast media, and all concluded that low-osmolal agents are safer. Publications comparing ionic and non-ionic low-osmolal versus iso-osmolal agents showed conflicting results(13–15)· However, two meta-analyses failed to demonstrate any difference between renal toxicity of those agents, except for one particular non-ionic low-osmolal agent (iohexol), that seemed to be more nephrotoxic[15,16].

Thus, recent guidelines recommend the use of low osmolality and iso-osmolality agents, since they are associated with a lower risk of kidney injury.

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■ Risk factors

The clinical significance of CIN heightens the importance of identifying patients with highest risk of developing this condition. So far, procedure and patient-related risk factors have been studied.

Procedure-related factors include:

1. The use of high-osmolality agents, as explained before;
2. The high volume of contrast media;
3. The number of procedures and repeated administration within 72 hours after initial exposure[17,18];
4. The local of administration, as it was also verified that intra-arterial administration of contrast media is associated with higher risk of CIN when compared to the intravenous route[19].

Patient-related factors include:

1. Pre-existing renal impairment, which is the strongest patient-related risk factor (higher baseline serum creatinine levels is associated with higher risk)[20,21];
2. Older age, especially those above 75 years old;
3. Other co-morbidities, as advanced chronic heart failure and anemia. Diabetes mellitus is also commonly considered an important risk factor for CIN. However, a randomized, double-blind multicenter trial performed more than 20 years ago showed that the incidence of CIN in diabetic patients with preserved renal function was low, proving that it is not an independent risk factor, in spite of contributing to CIN in patients with underlying CKD[10]. This means that among CKD patients, those with diabetes are at higher risk;
4. Volume depletion;
5. The use of nephrotoxic drugs, like non-steroidal anti-inflammatory drugs (NSAIDs), or even antibiotics[7,19,22].

■ Pathophysiological mechanisms

Although not completely elucidated, the pathophysiological mechanisms by which contrast agents cause kidney injury comprise hemodynamic and indirect effects, as well as direct effects[23,24].

Hemodynamic and indirect mechanisms include generation of reactive oxygen species (ROS) and vasoconstriction mediated by vasomotor molecules such as endothelin, nitric oxide and prostaglandins that reduce glomerular blood flow and medullary hypoxia. In addition, the increased blood viscosity induced by contrast media diminishes erythrocyte plasticity leading to microvascular thrombosis[24,25].

Direct mechanisms are related with an intrinsic cytotoxic effect on tubular epithelial cells, leading to cell apoptosis and necrosis, which, in turn, contribute to tubular obstruction, increased intratubular pressure and decreased glomerular filtration rate (GFR). It is still a matter of debate if contrast agents lead to epithelial necrosis or just functional changes in those cells, as recovery from CIN is much faster than recovery from acute tubular necrosis from other causes.

■ Preventive Strategies

In order to avoid CIN, many preventive strategies have been proposed over the years, including intravenous volume expansion, pharmaceutical agents and renal replacement therapies. The first step is to identify patients at risk, and CKD patients should be the target population for active preventive measures.

Although there are still some contradictory findings regarding the benefit of some of those prophylactic measures, current strategies compromise peri-procedural intravenous crystalloid[26,27] along with avoidance of nephrotoxic drugs and use of low or iso-osmolality contrast media in the lowest possible volume. According to American College of Radiology guidelines published in 2018, isotonic fluids are preferred and a protocol using intravenous isotonic saline at an infusion rate of 100 mL per hour for six to 12 hours before and four to 12 hours after the procedure is recommended[11].

Volume expansion

Over the years, multiple trials have compared the preventive efficacy of intravenous isotonic sodium bicarbonate with isotonic sodium chloride, given the hypothesis that urine alkalization reduces generation of ROS and lessens oxidative stress, a mechanism involved in the pathogenesis of CIN. Though there are some conflicting results[28,29], a double-blind two-by-two factorial design trial by Weisbord *et al*. found no benefit of intravenous sodium bicarbonate over intravenous sodium chloride for the incidence of CIN or for the prevention of death, need for dialysis or persistent kidney impairment at 90 days[30].

Despite current recommendations, a non-inferiority trial and its long-term follow-up (AMACING – A Maastricht Contrast-Induced Nephropathy Guideline) showed no significant difference between the incidence of CIN in the group receiving intravenous hydration and the group assigned to no prophylactic measures[31,32]. Nevertheless, this study had some limitations, including the small sample size, single-center, low rates of intra-arterial and interventional procedures, as well as, a small percentage of patients with severe CKD. Thus, it is impossible to conclude that volume expansion is ineffective based on these results.

Pharmaceutical agents

N-acetylcysteine is an agent presumed to reduce the incidence of CIN due to its vasodilatory and antioxidant effects[33]. Multiple trials and meta-analyses failed to reach a consensus on the role of this drug in CIN prophylaxis[34], but the PRESERVE (Prevention of Serious Adverse Events Following Angiography) trial showed no reduction of the primary 90-day composite end-point comprising death, need for dialysis or persistent impairment of renal function or in the incidence of CIN[30]. Hence, the routine administration of N-acetylcysteine is not advised despite being widely used due to its low costs and rare side effects.

Some observational studies also suggested that statins could have a protective effect given their pleiotropic properties (anti-inflammatory and anti-oxidant effects). Indeed, the PRATO-ACS (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Acute Kidney Injury and Myocardial Damage in

Patients with Acute Coronary Syndrome) study showed a significant lower incidence of CIN in patients treated with high-dose rosuvastatin[35]. These findings, however, were not corroborated in the prospective trial PROMISS (Prevention of Radiocontrast Medium-Induced Nephropathy Using Short-Term High-Dose Simvastatin in Patients with Renal Insufficiency Undergoing Coronary Angiography)[36]. Thus, further studies are needed in order to determine the role of statins in CIN prophylaxis.

Theophylline, a non-selective adenosine receptor antagonist, was thought to have a role in preventing CIN[37]; however, a meta-analysis performed in 2005 showed inconclusive results[38].

Diuretics and forced diuresis were studied as a means of preventing CIN, but failed to show any benefit. Both mannitol (an osmotic diuretic) and furosemide (a loop diuretic) were tested, due to their renal vasodilatory effects and promotion of tubular flow. However, these effects did not reduce the risk of CIN[39,40].

Renal replacement therapies

Extracorporeal blood purification therapies were also studied for the prevention of CIN. A meta-analysis performed by Cruz *et al*. concluded that these treatments do not have significant effect on the incidence of CIN[41,42], and thus it is not recommended to perform dialysis after contrast injection.

Current Paradigm

Despite all the previous reports published in the past decades that support the association of contrast media and renal function impairment, more recent studies have been questioning this evidence. In fact, the majority of these studies lack a control group of patients who is not exposed to intravenous contrast media. Moreover, they assume that any elevation of serum creatinine levels that meets the diagnostic criteria is a consequence of CIN, not accounting for fluctuations in creatinine levels that have been recognized as a common phenomenon in hospitalized patients or other causes of AKI[43,44]. The work of Newhouse[45] and Bruce[46] showed that the incidence of creatinine elevation in subjects who underwent unenhanced CT was similar to those who received intravascular iodinated contrast agents. These findings suggest that the incidence of CIN may be overestimated. However, those studies may have a selection bias in which higher-risk patients are less likely to be exposed to contrast material.

A meta-analysis performed by McDonald *et al*. comprising 25,950 patients failed to show a significant difference in the incidence of AKI, dialysis and death between patients who were subjected to procedures with intravenous administration of contrast material and controls[47]. This new evidence was corroborated by propensity-score matched studies that aimed to eliminate biases caused by comorbidities and confounding factors[48-51].

Although currently available evidence is insufficient to declare that contrast media are not nephrotoxic, patients should be carefully evaluated and assessed for comorbidities and factors that confer higher risk so that evidence-based preventive measures can be implemented.

MAGNETIC RESONANCE IMAGING AND NEPHROGENIC SYSTEMIC FIBROSIS

Given the widely known nephrotoxicity of radiocontrast agents, MRI scans enhanced with gadolinium-based contrast (GBC) agents have been considered a safe alternative to CT scans, when the need for contrast media is imperative. Meanwhile, concerns about gadolinium toxicity came to light and a new clinical entity was recognized as a consequence of exposure to this agent in CKD patients – nephrogenic systemic fibrosis (NSF)[52].

NSF, originally termed nephrogenic fibrosing dermopathy, was first reported in 1997[53]. In 2000, Cowper *et al*[54]. described the case of nine renal transplant recipients who required long-term dialysis, five patients with ESRD, and one patient with AKI identified with a skin condition characterized by thickening and hardening of the skin of the extremities, histologically similar to scleromyxedema.

Evidence linking NSF to GBC agents exposure emerged a few years later[55,56]. Marckmann *et al*. presented a description of 13 patients with end-stage CKD, all of which had been exposed to gadodiamide before the development of NSF. The time period between exposure and development of the first symptoms of the disease varied between two and 75 days[56].

Further evidence made the association clear when High *et al*. demonstrated that affected tissue of patients with NSF is approximately 35- to 150-fold higher than the level of retained gadolinium in the bone of healthy controls[57].

As a systemic disease, NSF not only is responsible for cutaneous hyperpigmentation and induration and joint contractures, but it also causes fibrosis of the left ventricular myocardium, pericardium, great vessels, interstitial pulmonary fibrosis and pulmonary hypertension. It has a significant burden in mortality, with a 24-month mortality rate of 48% versus 20% of controls[58].

This entity develops due to infiltration of affected tissues by macrophages and fibroblasts, which release profibrotic cytokines, as transforming growth factor- beta-1. The diagnosis is established with a skin biopsy showing fibrotic lesions, stained with CD34+ dermal dendritic cells.

Gadolinium-based contrast

GBC agents are nonradioactive, paramagnetic, non-tissue specific, hyperosmolal contrast agents, composed of gadolinium bound to a chelating ligand. They are classified according to their charge (ionic and non-ionic) and their chelating ligand (linear or macrocyclic)[11]. The chelating ligand is crucial to the molecule's safety, since free gadolinium is toxic, as it can precipitate in tissues and reduce neuromuscular transmission by blocking calcium channels. Ionic and macrocyclic agents are more strongly bound and, thus, more stable[59]. These agents are mostly excreted by the kidney, since they don't bind to proteins, although two of them are also excreted in bile.

They can be classified into three groups, according to their likelihood of causing NSF[38]:

– Group 1: molecules with a linear chelating agent and with a strong association with NSF. These agents are contraindicated in dialysis and acute renal injury patients and are not recommended in CKD patients with eGFR <30 ml/min;
– Group 2: most molecules with a macrocyclic chelating agent (except for one molecule – gadobenate), and a weak association with NSF;
– Group 3: newer agents, with insufficient data.

Risk factors for NSF

As with CIN, procedure and patient-related risk factors have been studied.

Procedure-related factors include:

1. The use of GBC agents from group 1, as explained before;
2. The use of GBC agents with linear chelating preparations;
3. The high volume and dose of the agent;
4. The intra-arterial route(60–63).

Patient-related factors include:

5. Pre-existing renal impairment. It is important to notice that patients at highest risk of developing NSF are those with underlying renal dysfunction. The majority of cases described occur in patients with end-stage CKD undergoing hemodialysis. However, there are some cases reported in patients with stage 4 and 3 CKD, as well as, patients with acute kidney injury or after renal transplant[64];
6. Other potential risks, not proved, are high phosphate or iron serum levels, metabolic acidosis, high-dose erythropoietin and concomitant use of lanthanum carbonate[65].

Preventive strategies

The main preventive strategy is avoiding Group I GBC agents or linear chelating GBC agents in patients with eGFR inferior to 30mL/min.

In dialysis patients, if GBC agents are indispensable, only Group II or III agents should be used, and hemodialysis should be performed immediately after (within 1 to 4 hours). A second dialysis session within 24 hours should be considered[66]. In peritoneal dialysis (PD) patients, a hemodialysis catheter should be placed, and two sessions should be performed after the MRI. If this is not possible, PD must be performed using a regimen of 10 to 15 exchanges per day for two days, with no dry period[67].

Further investigation is needed in order to find less nephrotoxic agents that can be an alternative to GBC agents. Ferumoxytol is a drug used as an iron replacement therapy in patients with chronic renal disease and, in spite of not being approved for use as an MRI contrast agent, has no known nephrotoxicity and may be considered when its clinical benefit outweighs the risk of allergic reaction[68]. Manganese-based complexes have also shown potential since they are cleared via biliary excretion, a particularly attractive feature in the context of renal compromise[69].

CONCLUSION

CIN has been widely accepted as a clinical entity responsible for increased risk of mortality, cardiovascular events, renal failure, and prolonged hospitalization. In spite of the current controversy regarding its actual incidence, it is important to recognize this condition and prevent it. As the understanding of its pathophysiological mechanisms and risk factors has arisen, new evidence about preventive strategies has also emerged, making it imperative to thoroughly evaluate patients at highest risk of developing CIN and implement evidence-based prophylactic measures.

It is also important to be aware of GBC agents' toxicity and increased risk of NSF in advanced stages of CKD. Further investigation is needed to find less harmful agents that can constitute an alternative in MRI enhancement.

Also, less harmful imaging techniques should be preferred whenever possible and advances in the investigation are needed in order to find new contrast media without toxic potential. In every patient, risk-benefit ratio should be assessed so that the fear of CIN or NSF doesn't limit correct diagnosis and appropriate and timely management.

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