RESEARCH PAPER

CONTRAST-INDUCED NEPHROPATHY: PATHOPHYSIOLOGY, PREVENTION, AND MANAGEMENT

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ABSTRACT

Contrast-induced nephropathy (CIN), also referred to as contrast-associated acute kidney injury (CA-AKI), is a significant iatrogenic complication observed following the administration of iodinated contrast media during radiological and interventional procedures. It is characterized by an acute deterioration in renal function, typically identified by a rise in serum creatinine occurring within 48–72 hours after contrast exposure. CIN remains an important cause of hospital-acquired acute kidney injury, particularly among high-risk populations such as patients with chronic kidney disease, diabetes mellitus, heart failure, dehydration, advanced age, and those receiving large volumes of contrast agents. The pathophysiology of CIN is multifactorial and involves renal vasoconstriction, medullary hypoxia, oxidative stress, endothelial dysfunction, and direct tubular epithelial toxicity. Preventive strategies are crucial and primarily focus on adequate hydration, minimization of contrast volume, use of low-osmolar or iso-osmolar contrast media, avoidance of nephrotoxic drugs, and identification of high-risk patients before procedures. Pharmacological interventions such as N-acetylcysteine, statins, sodium bicarbonate, and antioxidants have been investigated with variable outcomes. Management of established CIN is largely supportive and includes monitoring renal function, correction of electrolyte imbalance, optimization of hemodynamics, and renal replacement therapy in severe cases. Early recognition and implementation of evidence-based preventive measures can substantially reduce morbidity, mortality, prolonged hospitalization, and healthcare burden associated with CIN.

Keywords: Contrast-induced nephropathy, contrast-associated acute kidney injury, iodinated contrast media, acute kidney injury, renal toxicity, prevention, hydration therapy, oxidative stress.

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INTRODUCTION

One well-known cause of acute renal failure in a hospital setting is contrast-induced acute kidney damage (CIAKI), often referred to as contrast-induced nephropathy (CIN).[1] It has a low incidence in general population [2] (2%), but there are certain at risk groups in which it is more common. The patient demographic, baseline risk factors, and the criteria used to define CIN all influence the incidence of CIAKI, which varies across published studies in the literature. Serum creatinine (SCr) levels often rise within the first 24 hours following contrast exposure and peak up to five days later as part of the normal time course of CIAKI. A rise in SCr concentration of at least 0.5 mg/dL or at least 25% from the baseline within 48–72 hours following exposure to contrast media (CM) is the most widely accepted definition of CIAKI.[3]The following definition has been put out by the AKI Network: A sudden (within 48 hours) decline in kidney function, as seen by a decrease in urine output (confirmed oliguria of δ0.5 mL/kg/h for δ6 hours) or an increase in the SCr concentration of at least 0.3 mg/dL or at least 50% from baseline.[4]Over the past ten years, the incidence of contrast-induced nephropathy has dropped from 15% to 7%. This decline can be attributed to improved preventative measures and improved iodinated CM with lower renal toxicity. Loss of renal function may continue over time, and the CIN has an in-hospital mortality rate of ≥20%. Patients with contrast-induced nephropathy had a 5.5-fold higher chance of dying, even after controlling for concomitant conditions.[5]It has been shown that in-hospital mortality rates were 1.1% for patients with no CIN compared with 7.1% for those with nephropathy alone, and up to 35.7% for those with nephropathy requiring dialysis [6] and by 2 years, the mortality rate in patients who required dialysis was 81.2%. Although it is often less than 1%, the necessity for dialysis following CIN differs depending on each patient's risks at the time of contrast administration. In other trials, 3% of patients receiving primary percutaneous coronary intervention (PCI) for acute coronary syndromes and nearly 4% of patients with underlying renal impairment acquired CIN.[7]

METHODOLOGY

This narrative review was conducted to summarize current evidence regarding the pathophysiology, prevention, and management of Contrast-Induced Nephropathy (CIN), also referred to as Contrast-

Associated Acute Kidney Injury (CA-AKI). A comprehensive literature search was performed using major electronic databases, including PubMed, Scopus, Embase, and the Cochrane Library. Relevant articles published between 2000 and 2026 were identified to capture both landmark studies and recent advances in the understanding of CIN.

The search strategy incorporated combinations of Medical Subject Headings (MeSH) terms and keywords such as "contrast-induced nephropathy," "contrast-associated acute kidney injury," "radiocontrast nephropathy," "acute kidney injury," "iodinated contrast media," "pathophysiology," "prevention," "hydration therapy," "N-acetylcysteine," and "management." Boolean operators ("AND," "OR") were used to refine the search and improve relevance. Reference lists of selected articles and guideline documents were also manually screened to identify additional pertinent studies.

Studies eligible for inclusion consisted of original research articles, randomized controlled trials, observational studies, cohort studies, systematic reviews, meta-analyses, and international clinical guidelines addressing CIN pathogenesis, risk factors, preventive strategies, diagnostic approaches, and therapeutic management. Articles focusing exclusively on unrelated causes of acute kidney injury or non-iodinated contrast agents were excluded. Only studies published in English and involving human subjects were considered.

High-quality data from important nephrology, radiology, and cardiology guidelines—such as those from the American College of Radiology, European Society of Urogenital Radiology, and Kidney Disease: Improving Global Outcomes—was given special attention. Study design, patient population, diagnostic criteria, preventive measures, outcomes, and key conclusions were among the data taken from the chosen literature.

Thematic parts addressing epidemiology, pathophysiological mechanisms, risk factors, diagnostic criteria, preventive measures, treatment approaches, and new concepts were created by narratively synthesising the gathered material. This approach highlighted areas of disagreement and the need for more study while providing a comprehensive and therapeutically applicable summary of the state of knowledge about CIN.

Etiology

Pre-existing chronic renal disease is the most frequent cause of contrast-induced nephropathy. Following contrast exposure, approximately 8% of patients with estimated glomerular filtration rate (eGFR) between 45 ml/min/1.73m2 and 60 ml/min/1.73m2, 13% of patients with eGFR between 30 ml/min/1.73m2 and 45 ml/min/1.73m2, and 27% of patients with GFR less than 30 ml/min/1.73m2 experience contrast-induced nephropathy.[8]

Epidemiology

Diabetes and chronic renal disease are becoming more common. Following cardiac catheterisation and percutaneous coronary procedures, both of these are risk factors for acute renal damage. The incidence of contrast-induced nephropathy is estimated to be between 2% and 30%. The majority of instances can be fully reversed in two to four weeks. Only 1% to 4% of patients require renal replacement treatment, and less than half of those patients need it for an extended period of time. In the general population, the incidence of contrast-induced nephropathy is estimated to be more than 2%. However, the incidence might reach 20% to 30% in high-risk groups with kidney disease risk factors. It has been observed that using low osmolar contrast media reduces the risk of contrast-induced nephropathy.[9]

The third most common cause of iatrogenic acute renal damage is contrast-induced nephropathy. The most frequent cause is renal hypoperfusion, which results in either acute tubular necrosis or prerenal damage. Furthermore, the incidence of renal impairment is directly impacted by the quantity and kind of risk factors. The method also affects the incidence rate; reports in the literature range from 1.6–2.3% for diagnostic tests to 14.5% for coronary intervention.[10]

In patients older than 60 years, the incidence of CIN has been reported as 8%-16%. In patients with acute myocardial infarction who undergo coronary intervention, it has been shown that the age of 75 years or more is an independent risk factor for the development of CIN.

Pathophysiology of CIN

CIN's pathogenesis is complicated and only partially understood. Only the findings of mostly animal and laboratory studies can be used to guess on what precisely occurs inside a human kidney in vivo. A quarter of the cardiac output is sent to the kidneys during physiological rest. In order to maximise glomerular filtration and reabsorption of water and salts, the bulk is focused on the cortex. There is little blood supply to the medulla. Its purpose is to improve urine concentration and maintain osmotic gradients[11]. The juxtamedullary glomeruli's efferent arterioles supply blood to the renal medulla. These efferent arterioles give birth to the distal vasa recta (DVR) at the corticomedullary junction. Deeply penetrating the inner medulla, these DVR eventually create a capillary bed. Eventually, these capillaries come together to create the ascending vasa recta (AVR). The gradual transition from DVR to capillary to AVR is accompanied by histological alterations in the vessel wall's composition. [12]

In CIN, hypoxic medullary damage is crucial. Three distinct but possibly interrelated processes

are responsible for this: the effects of CM on haemodynamics, the impact of free radicals and reactive oxygen species (ROS), and direct tubular cell toxicity induced by CM molecules[13].

Haemodynamic effects

Regional PO2 levels in the renal medulla might be as low as 20 mmHg under healthy conditions. The deeper area of the outer medulla, which houses the metabolically active thick ascending limbs of the loop of Henle, is the most susceptible to hypoxia injury. Active salt reabsorption in this section of the tubular system creates an osmotic gradient, a process that needs a lot of oxygen[11]. When contrast media is injected intra-arterially, the haemodynamic response is biphasic, with a short-lived rise in renal blood flow followed by a long-term drop of 10–25% below baseline[14]. This mostly indicates a decrease in cortical blood flow because 10% of renal blood flow is medullary flow. There have been reports of declines in outer medullary PO2 of 50–67% following contrast medium delivery to 9–15 mmHg. A decrease in local microcirculatory blood flow and an increase in tubular cell oxygen demand work together to cause medullary hypoxia. [15]

Renal plasma flow, glomerular filtration, and urine output all momentarily increase when contrast media is injected. These effects increase with the osmolality of the injected contrast media. More sodium must be reabsorbed by distal tubular cells due to both osmotic load and the impact of endothelin release. As a result, more oxygen is consumed. [14]

Vaso-active mediators' reaction to contrast medium injection has been linked to the decrease in regional blood flow. In essence, vasoconstrictive and vasodilatative mediators are out of balance. The administration of contrast media has been linked to numerous mediators. Adenosine, dopamine, nitric oxide (NO), atrial natriuretic peptide (ANP), and prostaglandin E2 are important medullary vasodilatators. Vasconstrictors reduce glomerular filtration by acting more on the cortical arteries. Angiotensin II, endothelin, and vasopressin are strong vasoconstrictors[16]. Serotonin, bradykinin, leukotriens, histamine, and catecholamines are possible additional players in the pathophysiology, both dilatative and constrictive. It's unclear how much each mediator contributes. Additionally, distinct regional haemodynamic responses may be caused by the distribution of receptor mediator subtypes in the cortex and medulla.

The typical DVR diameter is between 12 to 18 µm, which is comparable to a red blood cell. It was demonstrated that micro-perfusion with iodixanol reduces diameter by 48% on isolated rat DVRs. This resulted from an increase in DVR's reactivity to angiotensin II and a decrease in NO generation. Iodixanol and angiotensin-II-induced vasoconstriction were avoided by adding a free radical scavenger[17]. Iodixanol had a stronger vasconstrictive effect on afferent arterioles than on efferent arterioles, according to additional studies from the same group. The elevated tone and responsiveness of afferent arterioles were explained by decreased NO availability and elevated superoxide content. [18]

Risk factors

The risk is extremely low, if not nonexistent, in patients with completely normal renal function (i.e., not only normal serum creatinine but also normal eGFR of >90 mL/min/1.73m2). However, see the warning about sudden changes in renal function brought on by variations in renal perfusion later.

2. Individuals who already have renal impairment are vulnerable. Patients with stage 1 or stage 2 CKD (GFR ≥60-89) have relatively little risk. While it is sense to assume that the danger rises as dysfunction grows, it is unclear if this is the case. The explanation is because the occurrence and severity of CIN are probably influenced by a wide range of other risk factors (e.g., nephrotoxic drugs, low cardiac output). The risk is increased roughly by a factor of 2 in patients with diabetes mellitus [19]. Again, the risk appears to be confined to those with CKD stage 3 or worse (GFR <60). This risk has been shown almost solely in patients with type I diabetes; the risk among the increasing population with type II diabetes is not clearly defined. There is likely to be an increased risk, as a function of the duration and severity of the diabetes.

Increasing age also is a risk factor, again only in those with compromised renal function. It is important to remember that renal function normally decreases with age, as reflected in both true GFR and eGFR but not necessarily in serum creatinine.

Preventive Strategies for Contrast-Induced Nephropathy

The best strategy for lowering the frequency and severity of Contrast-Induced Nephropathy (CIN) is still prevention, especially for high-risk patients having iodinated contrast media operations. The focus is on identifying sensitive individuals and putting evidence-based preventive measures in place before to contrast exposure because there is no proven treatment for existing CIN.

Risk Assessment and Identification of High-Risk Patients

Effective prevention of CIN requires early detection of patients at risk. Chronic kidney disease (CKD), diabetes mellitus, advanced age, dehydration, heart failure, hypotension, anaemia, and concurrent use of nephrotoxic medicines are major risk factors. Before administering contrast media, baseline renal function should be evaluated using serum creatinine and estimated glomerular filtration rate (eGFR). Individuals who have a lower eGFR are much more likely to acquire CIN, especially if they have diabetic nephropathy. [20]

Patients having coronary angiography and percutaneous coronary intervention frequently use risk stratification techniques like the Mehran Risk Score to determine the likelihood of CIN and direct preventive measures. [21]

Hydration Therapy

The foundation of CIN prevention is thought to be adequate hydration. Administering isotonic saline intravenously enhances renal perfusion, lessens renal vasoconstriction, dilutes contrast media inside renal tubules, and lowers oxidative stress. The majority of recommendations suggest administering isotonic saline (0.9% sodium chloride) at a rate of roughly 1 mL/kg/hour for six to twelve hours prior to and following contrast exposure[22]. Lower infusion rates may be required in patients with heart failure or cardiac dysfunction in order to prevent fluid overload.

Another hydration method that has been researched is sodium bicarbonate infusion. Alkalinisation of tubular fluid is the suggested method, which could lessen the production of free radicals. Regular use is still debatable, nevertheless, as clinical research has shown contradictory findings on its superiority over isotonic saline[23].

Optimization of Contrast Media

Reducing both the dose and nephrotoxicity of contrast media plays a major role in prevention. The smallest possible contrast volume should be used during diagnostic or interventional procedures. Repeated contrast administration within short intervals should be avoided whenever feasible[24].

Compared to previous high-osmolar contrast agents, contemporary low-osmolar and iso-osmolar nonionic contrast agents have a decreased nephrotoxic potential. In high-risk individuals, particularly those with pre-existing renal impairment and diabetes mellitus, iso-osmolar contrast medium may provide further renal protection.

Pharmacological Preventive Measures

A number of pharmaceuticals have been studied to prevent CIN. N-acetylcysteine (NAC) is the most extensively researched of these due to its vasodilatory and antioxidant qualities. Combining NAC with hydration therapy has been shown in certain studies to lower the incidence of CIN, although the outcomes are still variable among clinical trials (4). Because of its affordability and good safety profile, NAC is still widely utilised despite contradicting data.

Because of their anti-inflammatory and antioxidant properties, statins have also demonstrated possible renoprotective effects. Numerous studies have linked high-dose statin medication prior to cardiac operations to a lower prevalence of CIN.[22]

Other agents such as ascorbic acid, theophylline, and fenoldopam have been evaluated, but evidence supporting their routine use remains insufficient.

Avoidance of Nephrotoxic Drugs and Procedural Measures

Renal damage risk may be decreased by temporarily stopping nephrotoxic drugs prior to contrast exposure. Aminoglycosides, certain diuretics, and nonsteroidal anti-inflammatory medicines (NSAIDs) are among the medications that are frequently withheld. For senior patients and those with chronic kidney disease (CKD), a thorough medication evaluation is especially crucial[20].

In high-risk patients, alternate imaging methods that don't require iodinated contrast material should be taken into consideration whenever feasible. Contrast-sparing methods and close haemodynamic monitoring during angiographic procedures can further lower the risk of CIN.[22]

DISCUSSION

Despite improvements in contrast media safety and preventive measures, Contrast-Induced Nephropathy (CIN), also known as contrast-associated acute kidney damage, continues to be a major clinical problem. Patients with pre-existing renal impairment, diabetes mellitus, advanced age, and cardiovascular illness are more likely to experience CIN during radiological and cardiovascular operations employing iodinated contrast agents. The use of low-osmolar and iso-osmolar contrast media has reduced the prevalence of CIN, but it still contributes to longer hospital stays, greater rates of morbidity and death, and higher healthcare expenses. [25]

Renal vasoconstriction, medullary hypoxia, oxidative stress, and direct tubular epithelial damage are all part of the complex pathophysiology of CIN. Contrast media decrease vasodilatory chemicals like nitric oxide and prostaglandins while concurrently reducing renal blood flow through vasoconstrictive mechanisms mediated by endothelin and adenosine. Because of its comparatively low oxygen tension, the renal medulla is especially vulnerable to ischaemic damage as a result of these changes[26]. In addition, reactive oxygen species generated after contrast exposure contribute to cellular injury, inflammation, and apoptosis of tubular epithelial cells.

Since there is presently no proven cure for CIN, prevention continues to be the mainstay of treatment. Intravenous isotonic hydration is thought to be the most successful and scientifically supported preventative approach. Sufficient hydration minimises oxidative stress, lowers tubular concentration of contrast agents, and enhances renal perfusion. It is also highly advised to use low-osmolar or iso-osmolar nonionic contrast agents and minimise contrast volume, particularly in high-risk patients. Pharmacological treatments like statins and N-acetylcysteine have

demonstrated inconsistent results in various clinical trials, and their regular usage is still debatable. [27]

Particularly in critically ill patients with numerous comorbidities, recent research has questioned whether contrast media alone are the only cause of post-procedural acute renal damage. According to some researchers, confounding clinical circumstances may have historically led to an overestimation of the risk of CIN[28]. However, in order to reduce renal problems related to contrast delivery, current guidelines still place a strong emphasis on cautious patient selection, risk assessment, and the application of preventive strategies.

Future studies should concentrate on creating standardised diagnostic criteria, identifying new renoprotective treatments, and developing early biomarkers for renal injury. Prevention and management techniques may be further enhanced by developments in personalised risk prediction models and precision medicine. In general, lowering the burden of CIN and enhancing patient outcomes still depend on early identification of high-risk individuals and adherence to evidence-based preventive strategies.

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