



Contrast-induced nephropathy: a review of literature

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ABSTRACT

Today, radiological procedures using intravascular iodinated contrast media are being widely used for the diagnoses and treatment of various diseases, which highlight one of the main etiologies of contrast-induced nephropathy and hospital-acquired renal failure. Contrast-induced nephropathy development is associated with longer hospital stay, increase in both short- and long-term morbidity and mortality, in addition to greater health care costs.

The pathogenesis of contrast-induced nephropathy has not yet been fully explained in detail; however it is clear that the root concept is medullary hypoxia-induced renal tubular damage.

Chronic kidney disease and diabetes mellitus are the two most important intrinsic predisposing factors to contrast-induced nephropathy. As no treatment can specifically target contrast-induced nephropathy, the main goal for clinicians is prevention of the disease. While the best approach for achieving this goal is still controversial, optimization of the patients' circulating volume remains the only proven strategy to date. As contrast-induced nephropathy is a potentially preventable clinical condition, its better understanding will lead to better prevention of this disease.

Hereby, we aimed to discuss contrast-induced nephropathy from 7 different aspects in clinical practice: 1) clinical aspect, 2) prevalence, 3) pathophysiology, 4) contrast agents and renal cell apoptosis, 5) different contrast media, 6) prevention, and 7) treatment.

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Introduction

Nowadays, radiological interventions using intra-vascular iodinated contrast media are being widely used both for the diagnoses and treatment of various diseases. They are therefore regarded as one of the main etiologies of contrast-induced nephropathy (CIN) and hospital-acquired renal failure (1).

CIN, also called contrast induced acute kidney injury (AKI), is one of the major adverse events taking place following cardiac procedures. It is defined as an elevation of serum creatinine more than 25% or ≥ 0.5 mg/dl ($44 \mu\text{mol/l}$) from baseline within 48-72 hour (2,3) after exposure to a contrast agent compared to baseline serum creati-

nine values; accordingly, other etiologies for renal impairment including hypotension, urinary obstruction, nephrotoxins and atheromatous emboli should be initially excluded (4).

Despite low or iso-osmolar agents having been introduced and different preventive techniques being implemented, CIN is still the leading cause of iatrogenic AKI due to the expanding application of contrast media for imaging and intravascular procedures (5).

Chronic kidney disease (CKD) with impaired glomerular filtration rate (GFR) is the intrinsic predisposing factor of greatest importance. The

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risk of CIN development is in line with the degree of renal impairment, and it may exceed 50% in patients with a GFR of 10–15 ml/min. Diabetes is another major risk factor, and for every given baseline GFR in patients with CKD, the existence of diabetes doubles the risk of CIN development (6).

As no treatment can specifically target CIN, the main goal for clinicians remains prevention. While the best approach for achieving this goal is still controversial, optimization of the patients' circulating volume remains the only proven strategy to date (7,8).

The number of published studies on CIN has dramatically increased in the past few years. Because CIN is a potentially preventable clinical condition, the more CIN is understood, the greater the likelihood of reducing the risk.

Hereby, we aimed to discuss CIN from 7 different aspects which are of great importance in clinical practice: 1) clinical aspects, 2) prevalence of CIN, 3) pathophysiology, 4) contrast agents and renal cell apoptosis, 5) CIN association with different contrast media, 6) prevention of CIN by drugs and procedures, and 7) treatment.

Literature Review

Clinical aspect

CIN is the third leading cause of acute renal failure and a well-known adverse event of cardiac catheterization (8).

CIN is a potentially preventable clinical condition and is self-limited in most subjects. It is usually not diagnosed clinically as patients are mostly asymptomatic (2,4).

CIN is a transient and reversible form of acute renal failure. However, its development is associated with a longer hospital stay, an increase in both short- and long-term morbidity and mortality, in addition to greater health care costs. Treatment of CIN is mainly supportive, focused on precise fluid and electrolyte management; however certain cases may require dialysis. The available treatment options make prevention the cornerstone of management (2-5).

Incidence of contrast-induced nephropathy

The incidence of CIN has been obtained to be >2% in the general population but in high-risk individuals such as diabetics, those with a history of congestive heart failure, chronic renal impairment, and elderly, it has an incidence rate of more than 20% to 30% (9). The approximate incidence rate of CIN is about 150000 patients per year worldwide, among whom at least 1% undergo dialysis and a prolonged hospital stay (10).

CIN consists around 12% of all cases of in-hospital AKI and is also associated with an

overall in-hospital mortality rate of 6% (3). Renal hypoperfusion (42%) and postoperative renal injury (18%) precede CIN in this respect (4).

Coronary angiography and percutaneous coronary intervention (PCI) have the highest occurrence rates of CIN in between all procedures using contrast media for diagnostic or therapeutic purposes (2,3). The reported incidence of CIN after percutaneous coronary intervention (PCI) varies between 0 and 24%, depending on the prevalence of associated risk factors, with emergency PCI standing in the first place (2).

In patients with chronic kidney diseases (CKD), the incidence of CIN can be relatively high ranging between 14.8% to 55%, depending on the underlying conditions (3,11). On the other hand, patients with a GFR >60 ml/min, have a CIN risk of only 2% (3).

In a meta-analysis including 40 studies, the incidence of CIN was 6% after contrast enhanced computed tomography (CT) (12) and 9% after peripheral angiography (13), whereas a 4% incidence rate was found after intravenous pyelography (14).

The Mehran CIN-Risk score (MRS) was developed and initially validated for prediction of CIN after nonurgent percutaneous coronary intervention. This score includes 8 clinical and procedural variables: age >75 years, hypotension, congestive heart failure, intra-aortic balloon pump, serum creatinine, diabetes, anemia, and volume of contrast. In such cases a risk score of >6, 6 to 10, 11 to 16, and >16 indicates a CIN risk of 7.5%, 14%, 26%, and 57%, respectively (15). It has been proved that the risk of CIN has a direct association with the volume of contrast media delivered (4).

Pathophysiology

The pathogenesis of CIN has not yet been fully explained in detail; although it is clear that the root concept is medullary hypoxia-induced renal tubular damage (3). A rise in endothelin, adenosine, and free radical-induced vasoconstriction has been observed following CIN, while nitric oxide and prostaglandin-induced vasodilatation decrease. Subsequently, ischemia occurs in the deeper portion of the outer medulla (2-4). Moreover, contrast media have direct toxic effects on kidney tubular cells as vacuolization, change in mitochondrial function, and even apoptosis (4,16).

Impaired kidney function and diabetes mellitus (type 1 and type 2) are regarded as major risk factors for CIN. In high risk patients various GFR levels can be regarded as a risk factor as well. A GFR of less than 30 ml/min is associated with the highest risk (17).

Increased systemic oxidative stress, enhanced renine-angiotensine-aldosterone system activity,

and higher levels of endothelin-1 also contribute to an elevated risk of CIN (3).

Respectively, the most commonly proposed mechanisms include:

- Reduction in renal perfusion and renal medullary hypoxia which could be related to a decrease in vasodilators (nitric oxide or prostaglandins), or an increase in vasoconstrictors (adenosine and endothelin).
- Renal tubular damage due to direct toxicity of contrast media (CM) related to either harmful effects of free radicals or oxidative stress.
- Apoptosis may also play a role in the development of CIN (2,5).

Contrast agents and renal cell apoptosis

The administration of compounds with antioxidant features such as N-acetylcysteine (NAC) and ascorbic acid has been found to have an acceptable role in CIN prevention (4). Additionally, new clinical studies suggest sodium bicarbonate to have effective strategies in preventing CIN (18). It has been proposed that alkalinizing renal tubular fluid with bicarbonate could decrease injury (2-4).

Certain strategies should be taken into consideration when contrast agents are to be administered as follows: to reduce side effects, the CM should be prewarmed to 37 °C and injected with the lowest possible dosage. Injection should not be repeated within 72 hours of the first dose. Iso-osmolar CM iodixanol is suggested for high-risk patients with chronic kidney disease requiring intra-arterial administration. The use of nephrotoxic drugs should be stopped 2 days before the procedure. An optimal volume status should be established for all patients receiving CM. Twelve hours prior to CM administration parenteral isotonic saline with no diuretic and at a rate of 1 ml/kg/h should be started and continued for 24 hours in cases with no contraindication. In patients at a higher risk, bicarbonate infusion may be used as an alternative to isotonic saline. Moreover, oral N-acetylcysteine, due to low toxicity and low cost, beside parenteral hydration is also another preventive strategy for patients at risk. Hemodialysis is only considered in chronic kidney disease stage 4/5 patients when an access is available (3).

Nowadays, low-osmolar contrast media have achieved extensive clinical acceptance due to lower adverse events than high-osmolar compounds, mainly in high-risk subjects with a high serum creatinine level before the procedure (4).

Prevention of CIN

As the number of invasive procedures requiring contrast agents are expanding every day, prevention of their induced nephropathy is becoming

more urgent and a major concern. To date, different techniques have been developed to prevent this condition. The main strategies include antioxidants, intrarenal vasodilators, hydration therapy, and precise measurement of the amount of fluid excreted from a urinary catheter. Moreover, less toxic iodine-containing contrast media are also taken into practice (1).

Prevention of CIN is still a main concern during PCI as most patients whom undergo such procedures already have several comorbidities (19).

Several randomized controlled trials performed in the past 20 years have confirmed the beneficial role of intravenous fluid therapy in CIN prevention. Hydration has low cost and is usually risk-free. It is also of great importance to minimize the volume of contrast media and the frequency of its administration to ensure favorable image quality. In addition, in individuals with a low to moderate risk for CIN, free intake of salt and oral fluids may be recommended (4).

Jang et al. in a recent meta-analysis including 3609 patients from 19 trials concluded that bicarbonate-based hydration is superior to NaCl-based ones in patients undergoing exposure to iodinated contrast media. Accordingly, the authors recommend the administration of NaHCO₃ beside an NaCl hydration regimen (20,21).

In another study by Minsinger et al., the use of automated contrast injectors (ACIs) compared to manual injection in angiography showed a significant reduction in the volume of contrast delivered to the patient and the incidence of CIN (22).

Busch et al. concluded that preliminary studies are promising but further studies are required before recommending any strategy for CIN prevention in the routine care of patients undergoing primary PCI for ST-elevation myocardial infarction (8).

A meta-analysis performed on 496 patients by Wu et al. evaluating the effectiveness of NAC in CIN prevention among patients undergoing CT, recommends the wider use of NAC in high-risk patients undergoing contrast-enhanced CT (23).

In another study regarding oral NAC, it was suggested that as NAC has a very low toxicity and low cost, it can be used at a standard dose together with parenteral hydration for patients at risk of CIN (3).

Volume expansion can reduce the activity of the renine-angiotensin-aldosterone system, decrease vasoconstrictive hormones such as endothelin, increase sodium diuresis, decrease tubule-glomerular feedback, prevent tubular obstruction and ROS production, dilute the CM in the tubular cells, and therefore decrease the nephrotoxic effects on the tubular cells (3).

Treatment of CIN is mainly supportive; it involves careful fluid and electrolyte management. However,

in certain cases dialysis is performed. Taking together all the available therapeutic choices, prevention is highlighted as the cornerstone of management. As no incisive treatment exists for established CIN, one should always weigh the benefit for CM-based diagnostic studies against the risk of inducing CIN. Nevertheless, recurrent exposure to CM during a short period of time should be strongly avoided as far as possible (25).

The well-established approaches aimed at patient protection from unnecessary risk for CIN include careful assessment of renal function and avoiding the use of nephrotoxic medications, appropriate use of procedures requiring contrast media, and adequate hydration with isotonic solutions in the periprocedure period. Several studies have also demonstrated a clear benefit in urine alkalization with bicarbonate. However, this should be taken in the context of substantial heterogeneity in study protocols.

Limitations

A precise review the published trials to date shows design limitations contributed to their inconclusive findings. Such limitations include the small sample size, with a higher risk of type I and type II statistical errors and the enrollment of low-risk patients with unchanged baseline kidney function which may result in less adverse events occurrence and reduced generalizability to higher-risk populations (23).

Conclusion

Iodinated CM is the only agent available for diagnostic and interventional vascular procedures. CIN is a common cause of acute kidney functional impairment leading to considerable morbidity and mortality. Given its poor prognosis, the need for improved methods in its prevention is highly perspicuous.

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Conflict of Interest

The authors declare no conflict of interest.

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