Introduction

Contrast Induced Nephropathy (CIN) or Contrast Induced Acute Kidney Injury (CI-AKI) – as it is now referred to, is a common and preventable cause of acute kidney injury in hospitalized patients who get exposed to iodinated contrast agents. This leads to a considerable increase in the morbidity, mortality and length of the hospital stay. Preventive approaches involving risk stratification of patients before exposure to contrast agents, use of the lowest dose of iso-osmolar contrast agents and hydration are the cornerstones in reducing the risk of CI-AKI.

Previously lots of emphasis has been laid on the use of N-acetyl cysteine (NAC) in the prevention of CI-AKI. Is it a myth or reality? Nephrologists quite often get referrals for performing dialysis to negate the effect of contrast medium and returning to baseline within 7–10 days.

Multiple communities in nephrology and radiology are now adopting broader terminology – contrast associated acute kidney injury (CA-AKI) or post contrast AKI that refers to any AKI occurring after administration of iodinated contrast agent and that may or may not be causally related to contrast agent. The term CI-AKI should particularly be reserved for AKI that can be causally linked to contrast agent administration. Thus, the term CA-AKI includes both CI-AKI as well as other coincidental etiologies like hypovolemia, cardiac dysfunction and infection which can also cause renal dysfunction.

Role of Biomarkers in the Diagnosis of CI-AKI

Apart from serum creatinine, serum cystatin C can also be used for the early identification of patients with CI-AKI. In a study using cystatin C as an early marker, a cut-off increase in cystatin C concentration of ≥ 10% at 24 hours after contrast-media exposure was detected in 87 patients (21.2%) with a negative predictive value of 100 %. As seen in other cases of AKI, it appears that in patients with pre-existing renal dysfunction, cystatin C may be a useful marker for the early diagnosis of CI-AKI.

Many recent studies have shown the potential role of biomarkers in predicting CI-AKI. Increased urinary levels of kidney injury molecule-1 (KIM-1), IL-18, N-acetyl-β-d-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) can predict CI-AKI much before the rise of serum creatinine. Once these investigations become cheaper and have a shorter turnaround time (TAT), they will definitely play a vital role in the diagnosis and prognosis of CI-AKI.

Incidence of CI-AKI

It has been shown that in patients with normal renal function, even in the presence of diabetes, the risk of contrast-induced AKI is significantly higher. This risk is further increased in patients with pre-existing renal dysfunction. The incidence of CI-AKI has been reported to range from 1% to 20% with an overall incidence of 11% of AKI cases.

Definition and Relevance Of CI-AKI

CI-AKI or CIN is defined as an absolute increase in serum creatinine of ≥0.5 mg/dl or as a relative increase of ≥25% from the baseline within 48–72 hours of contrast exposure. It has been described as the third most common cause of AKI in hospitalized patients after decreased renal perfusion (prerenal) and nephrotoxic medication(s). It constitutes about 11% of AKI cases.

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Contrast Induced Acute Kidney Injury (CI-AKI) is one of the most common causes of acute kidney injury in hospitalized patients. These days, contrast agents are widely being used in both cardiology and radiology procedures. Old age, history of diabetes, heart failure, proteinuria and low blood pressure are some important risk factors in the pathogenesis of CI-AKI.

Apart from risk stratification and the use of low and iso-osmolar contrast agents, intravenous fluid hydration with crystalloids is the only recommended strategy for the prevention of CI-AKI. Agents like N-acetylcysteine (NAC), atrial natriuretic peptide, ascorbic acid, theophylline, and fenoldopam have failed to show any proven beneficial role in the prevention of CI-AKI. Though hemodialysis is still being perceived by many clinicians as the modality for contrast removal but prophylactic hemodialysis is now not recommended for the prevention of CI-AKI.

Abstract

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Incidence of CI-AKI

It has been shown that in patients with normal renal function, even in the presence of diabetes, the risk of
as compared to low and iso-osmolar osmolality have higher nephrotoxicity (Table 1). The contrast media with high osmolality are employed in relation to the use of nephrotoxic drugs.  

**Table 1: Differentiation of Contrast Agents**

<table>
<thead>
<tr>
<th>Osmolality (mOsm/kgH₂O)</th>
<th>High-osmolar (1500-2100)</th>
<th>Low-osmolar (500-900)</th>
<th>Iso-osmolar (290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionicity</td>
<td>Ionic</td>
<td>Non-ionic</td>
<td>Non-ionic</td>
</tr>
<tr>
<td>Number of Benzene Rings</td>
<td>Monomer</td>
<td>Dimer</td>
<td>Monomer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dimer</td>
</tr>
<tr>
<td>Viscosity (cP)</td>
<td>8.4</td>
<td>9.5</td>
<td>7.8-11.2</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>320</td>
<td>350-370</td>
</tr>
<tr>
<td>Iodine Content (mg/ml)</td>
<td>Diatrizoate (Gastrografin)</td>
<td>Ioxaglate (Hexabrix)</td>
<td>Iohexol (Omnipaque), Iopamidol (Visipaque)</td>
</tr>
</tbody>
</table>

**IODINATED CONTRAST AGENTS**

<table>
<thead>
<tr>
<th>Risk Factors Score</th>
<th>SUM</th>
<th>Class of risk (Total score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>5</td>
<td>Low (≤ 5)</td>
</tr>
<tr>
<td>IABP</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CHF (NYHA Class III/IV)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>4</td>
<td>Medium (6-10)</td>
</tr>
<tr>
<td>Anemia (hematocrit &lt;39% in men and &lt;36% in women)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Contrast media volume</td>
<td>1 for each 100 ml</td>
<td>High (11-16)</td>
</tr>
<tr>
<td>eGFR ≤ 20 ml/min/1.73m²</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>eGFR 20-40 ml/min/1.73m²</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>eGFR 40-60 ml/min/1.73m²</td>
<td>2</td>
<td>Very High (≥16)</td>
</tr>
</tbody>
</table>


CI-AKI is as low as 1–2%. However, the incidence may be as high as 25% in patients with pre-existing renal impairment or in presence of certain risk factors such as the combination of pre-existing renal failure and diabetes, congestive heart failure (CHF), advanced age, and concurrent administration of nephrotoxic drugs. Types of contrast agents

The term CI-AKI is generally employed in relation to the use of iodinated contrast media used for computed tomography (CT) scan. Various contrast agents being used are differentiated based on their osmolality (Table 1). The contrast media with high osmolality have higher nephrotoxicity as compared to low and iso-osmolar contrast agents. CI-AKI generally occurs after iodinated contrast agents, although gadolinium (Gd) based contrast agents used in MRI scans can also cause renal dysfunction apart from nephrogenic systemic fibrosis.

The pathophysiology of CI-AKI is multifactorial. Intrarenal vasoconstriction, generation of reactive oxygen species, and direct tubular damage are the predominant factors that lead to CI-AKI. Contrast agents increase the release of adenosine, endothelin, and free radical species which induce vasoconstriction coupled with impaired nitric oxide and prostaglandin-induced vasodilatation. These mechanisms cause ischemia in the deeper portion of the outer medulla, an area with high oxygen requirement and remote from the vasa recta supplying the renal medulla with blood. Contrast agents retained in kidneys have direct toxic effects on renal tubular cells causing vacuolization, altered mitochondrial function and apoptosis (Figure 1).

**Assessment of Risk Factors**

In the current scenario, radiological evaluations which require contrast media are generally performed in the elderly population, many of whom already have CKD and diabetes—the principal risk factors for CI-AKI. It is, thus, of utmost importance to screen patients at risk for CI-AKI before the procedure.

A CI-AKI Consensus Working Panel has shown that the risk of CI-AKI becomes clinically important when the baseline Serum creatinine concentration is ≥ 1.3 mg/dl in men and ≥ 1.0 mg/dl in women, equivalent to an eGFR ≤ 60 ml/min per 1.73 m². Apart from pre-existing kidney disease, other major risk factors for developing CI-AKI include diabetes, congestive heart failure (CHF), advanced age, volume depletion and large volume or high osmolality of the contrast agent. Diabetes acts as a risk multiplier for CI-AKI. Concomitant use of nephrotoxic medication like Non-Steroidal Anti-Inflammatory drugs (NSAIDs), aminoglycosides, amphotericin B, high doses of loop diuretics, and antiviral drugs like acyclovir are additional risk factors.

Most risk factors for CI-AKI can be detected by a thorough history-taking and examination, and the risk rises exponentially with the number of risk factors present. Validated risk-prediction models can also help us to predict the risk of CI-AKI. A risk score for prediction of CI-AKI after the percutaneous coronary intervention has been reported by Mehran et al (Table 2). A risk score of <6 (Low), 6 to 10 (Medium), 11 to 16 (High), and >16 (Very High) indicates a risk for CI-AKI of 7.5%, 14%, 26%, and 57%, respectively.

**Preventive Strategies**

Prevention is always better than cure and this certainly holds true for CI-AKI as well. An alternative and safer modality of imaging that doesn’t involve use of the contrast agent like MRI is preferable. In high-risk cases,
we should use a minimal quantity of contrast volume and preferably use iso-osmolar or low-osmolar contrast agents. Other nephrotoxic drugs like NSAIDS, aminoglycosides or high dose loop diuretics should be discontinued.

**Role of Fluid Hydration**

Extracellular fluid expansion with intravenous crystalloids, either isotonic sodium chloride or sodium bicarbonate is the most important preventive measure. Recommended regimens for volume replacement for patients undergoing contrast administration include normal saline administered at 1 mL/kg/h for 3–12 hours pre-procedure and continued for 6–12 hours post-procedure. There is no clear evidence to guide the choice of the optimal rate and duration of fluid infusion in CI-AKI prevention. Recently published PRESERVE Trial concluded that there was no significant benefit of intravenous sodium bicarbonate over intravenous sodium chloride among patients who were undergoing angiography for the prevention of death, need for dialysis, or a persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury. Oral volume expansion may have some benefit, but there is not enough evidence to show that it is as effective as intravenous volume expansion. Thus, hydration with oral fluids alone is not recommended.

Extracellular volume expansion counteracts both the intrarenal vasoconstriction and the direct tubulotoxic effects of contrast agents that play a role in the pathophysiology of CI-AKI. Volume expansion may also directly reduce cellular damage by dilution of the contrast medium and decreases viscosity, particularly in the medullary tubular segments.

*Renal Guard therapy* is an automated and personalized hydration system that has shown superiority in preventing CI-AKI by ensuring a stable urine volume without a reduction in body’s hydration during treatment using contrast media. This system monitors the infusion rate of fluids, urine volume from the catheter, and weight changes. This system allows a high urine flow rate (≥300 mL/h) to be achieved, while simultaneously balancing urine output and venous fluid infusion volume of normal saline to prevent hypovolemia until 4 h after cardiac catheterization.

POSEIDON trial showed that left ventricular end-diastolic pressure (LVEDP) guided fluid administration is safe and effective method of preventing contrast-induced acute kidney injury in patients undergoing cardiac catheterisation.

**Role of N-acetylcysteine (NAC)**

N-acetylcysteine (NAC) is an excellent antioxidant and scavenger of free oxygen radicals. However, it has failed to show conclusive evidence of a protective effect in CI-AKI. Various meta-analyses have shown insignificant results regarding the efficacy of NAC in CI-AKI. The second arm of the PRESERVE trial also showed no benefit of oral acetylcysteine over placebo in terms of endpoints. Recently published Japanese guidelines also concluded that the strength of the evidence concerning the preventive effect of NAC on CI-AKI is low, and recommend against the routine use of NAC as a preventive strategy. NAC is inexpensive and appears to be safe but, it may have some detrimental effects on myocardial and coagulation function at a higher dosage. Hence, oral NAC (600-1200mg twice a day for 2-3 days) can be given along with intravenous volume expansion.

**Role of Statins**

The proposed hypothesis for the role of statins in reducing the risk of CI-AKI is by their anti-inflammatory and antioxidant properties. A majority of studies that compared statins with placebo had a target population who had a normal renal function, and only a few studies enrolled patients with renal failure. PROMISS (Prevention of radiocontrast medium induced nephropathy using short term high dose simvastatin in patients with renal insufficiency undergoing coronary angiography) study failed to show any significant difference between simvastatin and placebo arms. Meta-analyses of various studies on the effectiveness of statins showed a risk of bias and weak evidence and thus need for future studies. Therefore, the routine use of statins for CI-AKI prevention cannot be recommended at present.

**Role of Other Pharmacological Agents**

Other agents like atrial natriuretic peptide (ANP), ascorbic acid, theophylline, and fenoldopam have failed to show any benefit against CI-AKI and thus, are not recommended.

*ANP* has been reported to be beneficial in AKI post-cardiac surgery due to its natriuretic, vasodilatory (particularly on afferent arteriole) and anti-RAS effects. A study by Morikawa et al showed that systemic protocol of continuous intravenous hydration along with ANP is a safe and effective method of preventing CI-AKI but it was a non-blinded single-center study. A recent study by Okumura et al showed that ANP had no prophylactic effect against CI-AKI. Therefore, the use of ANP for prophylaxis of CI-AKI is not recommended.

*Ascorbic acid* has antioxidant properties. But recent meta-analysis of 6 randomized control trials failed to show any significant difference in risk reduction of CI-AKI by ascorbic acid and the strength of evidence was low. So, its use is not yet recommended for the prevention of CI-AKI.

The efficacy of *Theophylline*, an adenosine antagonist, in preventing CI-AKI has been compared by two major meta-analyses, one in 2005 (nine RCTs, 585 patients), and another in 2008 (six RCTs, 629 patients). Both of these showed an insignificant trend toward a protective effect of theophylline against CI-AKI.

Similarly, the use of *Fenoldopam* which is a selective dopamine A1 receptor agonist is not recommended. It might increase renal medullary blood flow, but the prospective randomized trials have shown no significant effects.

**Role of Prophylactic Dialysis Modalities**

Nephrologists quite often get consults from other clinicians for dialysis therapy soon after the administration of contrast material. Many clinicians perceive that extracorporeal therapies can potentially remove contrast agents and thus prevent CI-AKI. It could theoretically be anticipated that high-flux membranes used in hemodiafiltration (HDF) modalities should be able to remove contrast media more efficiently than low-flux membranes used in routine intermittent hemodialysis (HD). Cruz et al in their meta-analysis of 11 studies (8 of HD and 3 of HDF) concluded that there are no beneficial effects of these modalities as compared to standard fluid hydration.
renal dysfunction and low cardiac output, fluid hydration is generally done at a very lower rate of infusion to avoid the risk of pulmonary edema and overhydration, whereas pre dilution hemofiltration can safely provide required hydration to such patients. In post hoc analysis by Cruz et al, renal replacement therapies were found to be associated with a harmful trend in CKD stage 3 while no clear benefit could be demonstrated in reducing the risk of CI-AKI in CKD stages 4-5 patients. 37

However, there is no conclusive evidence that prophylactic IHD or HDF will prevent renal injury and therefore these modalities are not recommended.17,42 HD should of course be performed for other routine indications such as hyperkalemia, fluid overload etc. rather than as a tool for removing contrast agents to prevent CI-AKI.

**Should ACEI/ARB be stopped before the use of iodinated contrast agents?**

There is no conclusive evidence that RAAS inhibitors (ACE inhibitors and angiotensin receptor blockers) increase the risk of CI-AKI.43,44 In various recent meta-analyses, the use of RAAS inhibitors have not shown any significant effect on CI-AKI in patients undergoing cardiac interventions.35,46 Therefore, discontinuation and reduction in the dosage of these drugs are not required.27

**Should Biguanides (metformin) be stopped before the use of iodinated contrast agents?**

Biguanides (Metformin) can increase the risk of developing lactic acidosis with a transient impairment in kidney function which occurs after the use of iodinated contrast agents. About 8% of the total cases of metformin-induced lactic acidosis had an association with CI-AKI.47

While administering an iodinated contrast media, it is recommended that we should temporarily discontinue or reduce the dosage of biguanides to prevent lactic acidosis.27,48

**Nephrotoxicity of Gadolinium (Gd) Chelates Used In MRI**

Gd chelates are widely used as MRI contrast agents and are considered to have a good overall safety profile as compared to iodinated contrast media. However, Perazella et al summarized many recent studies which raised the possibility of its nephrotoxicity.31 After that, the US FDA requests all the new labels of Gd based contrast describe the risk for nephrogenic systemic fibrosis (NSF) following exposure in patients with a GFR ≤ 30 ml/min per 1.73 m2. In CKD stage 5 patients, the half-life of Gd is increased up to 30 hours, but the relatively small molecular weight (500 Da), a small volume of distribution, and minimal protein binding make Gd chelates ideal for removal with hemodialysis (HD). So, patients on maintenance HD should be considered for dialysis post-exposure.17 However, there is no data that supports prevention of NSF or nephrotoxicity after hemodialysis.

**Conclusion**

Contrast induced acute kidney injury continues to be one of the most common causes of AKI in hospitalized patients. Patients with pre-existing renal dysfunction, diabetes, advanced age, and intra-vascular volume depletion are at high risk for developing CI-AKI. There is no definitive treatment available once AKI sets in and therefore, prevention strategies (Table 3) and risk stratification are very important. Extracelluar volume expansion with intravenous normal saline is the best available solution for the prevention of CI-AKI. Recent studies have failed to show the benefit of NAC but as it is inexpensive and relatively safe, oral NAC can be considered together with intravenous fluid hydration. Finally, there is no benefit of pre-emptive or prophylactic dialysis therapy and it is not recommended. We require more trials to probe the role of HD (hemodiafiltration) in the prevention of CI-AKI. In high-risk patients, we should consider a safer alternative imaging strategy. MRI gadolinium-based contrasts are relatively safer, though there is a risk of nephrogenic systemic fibrosis in patients with renal dysfunction when the estimated GFR is ≤ 30 ml/min/1.73m2. To avoid the risk of NSF in dialysis patients with no residual renal function (no urine output) if contrast administration is required, CT is clearly preferred over MRI.

**References**


**Table 3: Strategies to prevent Contrast Induced Acute Kidney Injury**

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>To identify high risk patients – Old age, Diabetes, CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Hydration</td>
<td>Intravenous fluid hydration – either with isotonic sodium chloride or sodium bicarbonate 37, Oral fluid hydration alone – Not Recommended 42</td>
</tr>
<tr>
<td>N-acetylcysteine (NAC)</td>
<td>Oral NAC – No conclusive evidence, can be given in addition to IV fluid hydration 22,27</td>
</tr>
<tr>
<td>Contrast Agent</td>
<td>Dose – Minimal Type – Low or Iso – Osmolar contrast agent 27</td>
</tr>
<tr>
<td>Nephrotoxic Agents</td>
<td>NSAIDS, aminoglycosides or high dose loop diuretics etc. should be stopped 27</td>
</tr>
<tr>
<td>ACE inhibitors / ARBs</td>
<td>Reduction of dosage not required 43,44</td>
</tr>
<tr>
<td>Biguanides (Metformin)</td>
<td>Temporarily withdrawal or reduction in dosage of biguanides 27,46</td>
</tr>
</tbody>
</table>

17,27,43,48


