

INTRODUCTION

The numbers of procedures requiring contrast media, one of the most important and modifiable causes of acute kidney injury (AKI) are increasing. Over 30 different definitions of AKI have been used in published literature. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, AKI is defined by any of the following criteria; rise in serum creatinine by at least 3 mg/dl within 48 hours or at least more than 1.5 times the baseline level within 7 days or urine volume less than 0.5 ml/kg/hr for six hours.

The term "contrast induced AKI" is preferred over other terms such as "contrast induced nephropathy", "acute renal failure" or "worsening of renal failure" because "injury" reflects wide pathological spectrum which includes subclinical injury with preserved renal function.

The incidence of contrast induced AKI is about 2% in general population; however, presence of risk factors increases the rates of contrast induced AKI. Presence of both chronic kidney disease and diabetes mellitus significantly increases the risk and the incidence may reach as high as 50% if there are multiple risk factors.

Contrast media can cause acute renal failure, increase in hospital stay, increase incidence of cardiovascular events and mortality. Even transient renal dysfunction after contrast induced AKI can have adverse impact on the prognosis. Considering serious consequences, better preventive strategies are required for improving clinical outcomes in patients who have high risk of developing AKI.

Table 1: Biomarkers for early detection of AKI

Renal region	Biomarker
Glomerulus	Total protein, urinary cystatin C, beta 2-microglobulin, alpha 1-microglobulin, albumin
Proximal tubule	Kim-1, Clusterin, NGAL, GST-alfa, beta2-microglobulin, alpha 1 microglobulin, NAG, Osteopontin, Urinary cystatin C, Netrin-1, HGF, Cyr61, NHE-2, Exosomal feutin-A, L-FABP, Albumin
Loop of Henle	Osteopontin, NHE-3
Distal tubule	Osteopontin, Clusterin, NGAL, H-HABP, Calbindin D28
Collecting duct	Calbindin D28

CHALLENGES IN THE DIAGNOSIS OF AKI

Age, gender, race, muscle mass, diet and nutritional status can affect production of creatinine. Similarly, tubular secretion of creatinine can be affected by bilirubin toxicity or use of certain drugs like cimetidine. Laboratory variability due to differences in assay calibration and factors affecting extra-renal elimination of creatinine can affect creatinine level. These are the limitations for use of definition of AKI based on serum creatinine level. Moreover, glomerular filtration rate (GFR) levels can be sustained by renal functional reserve despite kidney injury. It is therefore important to recognise the possibility of acute renal deterioration without changes in serum creatinine. Renal functional reserve is lost with repeated renal injury. The process should be considered as a continuum from the increased risk to the final stages of kidney damage. Considering the limitations of serum creatinine in AKI continuum, biomarkers (table 1) of early injury could help in early identification of AKI diagnosis and timely intervention.

Biomarkers can be combined with functional criteria in THE definitions of AKI. This might help in early diagnosis, timely intervention and better prognosis. Wide availability of facilities to perform these tests and cost are the limitations for use of biomarkers. Moreover, the current evidence for use of biomarkers for staging is insufficient.

TYPES OF CONTRAST MEDIA

The profile of contrast media differs based on their pharmacological properties such as structure, ionicity, iodine content and osmolality. Based on the osmolality, the contrast media can be classified as "high osmolar", "low osmolar" and "iso-osmolar" agents. The examples of high osmolar agents are diatrizoate, iohalamate and ioxithalamate. Iohexol, ioversol and iopamidol are low osmolar agents while iodixanol is an iso-osmolar agent.

Although the exact mechanism of contrast induced AKI is not completely understood, several factors have been suggested to mediate the impact of hyperosmolality on renal function. Diuretic effect stimulating a tubuloglomerular feedback mechanism resulting in reduced GFR, decreased renal blood flow due to alterations in vasoconstriction mediated by adenosine, endothelin and nitric oxide and altered erythrocyte morphology affecting capillary perfusion can potentially affect renal functions.

CONTRAST INDUCED AKI

The risk of AKI risk may be procedure dependent.

The rates of contrast induced AKI following coronary angiography have been reported to be higher than those following contrast-enhanced computed tomography which might be related to more co-morbidities in patients requiring coronary angiography and larger dose of contrast media during angiography. However, the risk of contrast induced AKI cannot be ignored in patients undergoing contrast-enhanced computed tomography procedures, considering their widespread and increasing use.

MANAGEMENT OF PATIENTS RECEIVING IODINATED CONTRAST MEDIA

The management of patients receiving iodinated contrast media should at least be based on eGFR. Patients with eGFR less than 30 ml/min need hospitalization. Adequate hydration should be maintained and plans be made in case dialysis is required. In patients with eGFR more than 60 ml/min (if receiving intra-arterial) or more than 45 ml/min if receiving intravenous contrast media, may require withdrawal of metformin. For patients with eGFR between these limits, nephrotoxic drugs and metformin should be stopped, adequate hydration should be maintained.

CHOICE OF CONTRAST AGENT

Studies consistently show a benefit of using low-osmolar contrast media over high-osmolar contrast media in terms of rates of contrast induced AKI. Iodixanol is associated with lower risk as compared with iohexol. Iso-osmolar or low osmolar contrast agents are generally used for diagnostic/interventional procedures. Iso-osmolar or low osmolar contrast agent other than iohexol can be used for percutaneous coronary intervention.

MEASURES TO PREVENT CONTRAST INDUCED AKI

The general principles of contrast-induced AKI management are similar to the management of other causes of AKI. Prevention of AKI is the key.

Dose of Contrast Media

Dose of contrast media should be used based on the renal function and interventional or diagnostic requirements. Lowest possible dose of contrast media should be used to avoid risk of severe AKI.

Hydration

Adequate hydration especially intravenous fluids are the key for prevention of contrast induced AKI, hence it is important to ensure adequate hydration. Isotonic intravenous fluids should be given before and continued for several hours after contrast administration. For outpatients the fluids can be administered at the rate of 3 mL/kg over one hour pre procedure and 1-1.5 mL/kg/hr during and for 4-6 hrs post procedure (min 6 ml/kg post procedure) whereas for hospitalized patients, the rates can be 1 mL/kg/hour for 6-12 hrs before, during and after procedure

Hydration with sodium bicarbonate is associated with a significant decrease in the incidence of contrast induced AKI compared with normal saline, but there is no

significant difference in the rates of post-procedural death or the requirement for renal replacement therapy.

Left ventricular end-diastolic pressure can be useful guide for fluid replacement. Renal guard system is a device which can guide fluid replacement in setting of forced diuresis.

Avoid Nephrotoxic Medicines

Nephrotoxic drugs such as non-steroidal anti-inflammatory drugs, aminoglycosides, ciclosporin, tacrolimus, and amphotericin B should be avoided. Loop diuretics should be stopped at least two days before the intervention, if possible, while chemotherapies (especially platinum-based) should be stopped at least seven days before. The risk associated with angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers is not clear. Metformin is not directly nephrotoxic, but due to the risk of accumulation of lactic acidosis, it should be stopped at least two days before administration of contrast media.

Pharmacological Prophylaxis

There is no convincing evidence to support use of pharmacological agents for prophylaxis of contrast induced AKI. Some agents (e.e. iloprost, N-acetylcysteine, statins) have shown preliminary evidence of prophylactic benefit, but further investigation in large-scale clinical trials are required before recommending them for the prevention of contrast induced AKI.

Acetylcysteine is an antioxidant having vasodilatory properties. There are conflicting results with use of acetyl cysteine. Acetylcysteine (1200 mg BD orally) may be administered orally a day before and on the day of procedure in high risk patients considering its potentially benefits, well tolerated safety profile and cost. However, it should always be used with hydration and iso-osmolar agents. Intravenous acetylcysteine, mannitol or other diuretics should not be used for the prevention of contrast nephropathy

Hemodialysis/Hemofiltration

These procedures do not provide significant benefit versus standard medical therapy in reducing the incidence of contrast-induced AKI. However, some centres perform hemodialysis within 24 hours post contrast administration.

Remote Ischemic Preconditioning

Induction of transient nonlethal ischemia of an organ can protect against subsequent ischemic injury. Methods of induction of ischemia include intermittent arm ischemia by blood pressure cuff inflation and deflation and balloon during percutaneous coronary intervention. Larger studies required before such procedures are recommended.

SUMMARY

Use of contrast media for various procedures is common and is rising. Contrast induced AKI is associated with significant burden on patients because of its hospital complications and increased mortality. The risk of AKI is affected by the quantity and type of contrast media

602 used and concomitant conditions. The measures to reduce risk of AKI include identification of patients at risk, use alternative imaging methods, selection of dose of contrast media based on renal functions and diagnostic/interventional need, selecting iso-osmolar or low-osmolar contrast media, discontinuation of nephrotoxic drugs and ensuring adequate hydration. If there is no contraindication, use isotonic intravenous fluids before and continue for several hours after contrast administration. Acetylcysteine (1200 mg BD orally) may be administered a day before and on the day of procedure. Intravenous acetylcysteine, mannitol or other diuretics should not be used for the prevention of contrast nephropathy. Prophylactic hemofiltration or hemodialysis in stage 3 or 4 CKD has no role in prevention of contrast associated AKI. Similarly, there is no role of early dialysis post contrast exposure in CKD stage 5.

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