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Nephrotoxicity Related to Iodinated-Based Contrast Media: From Pathophysiology to Management

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Abstract

Contrast Induced Nephropathy (CIN) or Contrast Induced Acute Kidney Injury (CI-AKI) is defined as sudden deterioration of renal function which is caused by administration of contrast media. Iodinated Contrast Media (ICM) is frequently used to enhance anatomical structure in medical imaging, for both diagnostic and therapeutic procedure, such as angiography, urography, and coronary intervention. The pathophysiology of nephrotoxicity related to ICM has not been completely understood. Hemodynamic changes, direct tubular cell toxicity and oxidative stress may contribute to pathophysiology of CI-AKI. Screening patient's risk factors, selecting contrast and avoiding nephrotoxic drug are several ways to be performed prior to administration of ICM to avoid CI-AKI. In addition to fluid administration and hemodialysis, medications such as N-acetylcysteine, statins, furosemide and nebivolol can be used to manage CI-AKI.

Keywords: Iodinated Contrast Media, Contrast Induced Acute Kidney Injury, Nephrotoxicity

Introduction

Iodinated Contrast Media (ICM) is frequently used to enhance anatomical structure in medical imaging, for both diagnostic and therapeutic procedure, such as angiography (vascular visualization of internal organ in computed tomography), urography (imaging of the urinary tract), and coronary intervention. However, like any other pharmaceutical in clinical practice, ICM also possess its beneficial and adverse side effect which should be aware of nephrotoxicity effect following intravascular administration of ICM.[1]

Contrast Induced Nephropathy (CIN) or Contrast Induced Acute Kidney Injury (CI-AKI) is defined as sudden deterioration of renal function which is caused by administration of contrast media, that cannot be attributable by other sources.[2]

Recent metadata in 2017, by collecting 5.9 million registry data, found 5.5% patient was developed AKI after receiving ICM at any type and route.[3] From the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial, which studied the overcome at patients with CKD undergoing cardiac angiography, CI-AKI is occurred in 9% of all

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participants.[4] However, other retrospective study of 6902 patients with Chronic Kidney Disease (CKD) showed no difference to Acute Kidney Injury (AKI) in patient who recieved intravenous CM on CT scan compared with patient who underwent non-contrast CT. Both group had an average creatinine rise of 0.3 – 0.4 mg/dL after contrast administration.[5]

Although CI-AKI remained controversial, this adverse side effect is faced by practitioner. However, as a physician should be responsible to the administration of CM to the patient. The incidence of CI-AKI may decrease as more physician recognize the risk and prevention.[6] Therefore, the pathophysiology, clinical presentation, risk assessment, and management of CI-AKI should be understood to reduce the severity of this nephrotoxicity effect.

Iodinated Contrast Media (ICM)

Iodinated Contrast Media (ICM) are soluble contrast media containing iodine that are given to patients to enhance the ability to visualize blood vessels and organs on medical images, such as X-Ray or Computed Tomography (CT) scan. Iodine itself is substance with high atomic number that absorb x-ray, with atomic weight 127.[7] ICM has different osmolalities. According to their osmolalities, ICM is divided into three types: (1) ionic High-Osmolar Contrast Media (HOCM) have an osmolality 1500 - 1800 mOsm/kg, five to eight times plasma osmolality (2) non ionic Low-OCM (LOCM) have an osmolality 600 - 850 mOsm/kg, two to three times plasma osmolality (3) nonionic iso-OCM (IOCM) have an osmolality ~290 mOsm/kg similar to plasma. HOCM are known to be more cytotoxic in vitro on proximal tubular cells than LOCM or IOCM.[7, 8]

Table 1: Types of Iodinated Contrast Media (ICM)

Class of Contrast Agent	Type of Contrast Agents	Iodine/Particle Ratio	Osmolality (mOsm/ kgH_2O)
Ionic High-Osmolar Contrast Media (HOCM) monomer	Diatrizoate (Renografin)	1.5	1870
	Ioxithalamate (Telebrix)	1.5	2130
Non-ionic Low-Osmolar Contrast Media (LOCM) monomer	Iohexol (Omnipaque)	3	780
	Lopamidole (Isovue)	3	790
	Lomeprol (Iomeron)	3	620
	Leversol (Optipray)	3	790
	Lopromide (Ultravist)	3	770
	Iopentol (Imagopaque)	3	810
Non-ionic Iso-Osmolar Contrast Media (IOCM) dimers	Iodixanol (Visipaque)	6	290
	Iotrolan (Isovist)	6	290

These contrast media mainly used intravascularly for angiography and computed tomography, but since they are mainly excreted by the kidney, it also used for urography. Iodinated water soluble contrast media is preferred to water insoluble contrast media to outline cavities.[9] These are examples of the usage of ICM to outline anatomical structure of cavities in clinical practice:

- Cholesystography requires an ICM that is excreted mainly by the liver, iodipamide and ioglycamide have been long preferred, iodoxamate and iotroxate are more efficiently excreted by this route.[10]
- In gastrointestinal tract, insoluble barium sulfate is still mainly used, but water soluble ICM may be considerable in special circumstances.[10]
- For Retrograde urography, many different water soluble ICM can be used, since they are diluted sufficiently.[10]

- Hysterosalphingography is mostly performed with LOCM.[10]

Pathophysiology

The mechanism of nephrotoxicity related to ICM has not been fully explained, however there are several factors may contribute to this event.

Hemodynamic Changes

The IV injection of ICM changes the vascular dynamic. After the administation of contrast, the renal bloodflow is initially increase followed by prolonged decrease in bloodflow or constriction of renal vessels. Contrary, the extrarenal bloodflow initially decrease followed by prolonged increase in bloodflow or dilatation of extrarenal vessels. These opposing conditions cause the elevation of renal vascular resistance, decreasing of renal blood flow, and decreasing of glomerular filtration rate (GFR).[11,12]

The most affecting part in renal, due to decreasing of renal blood flow is the medulla. In normal conditions, the medullary oxygen tension is 30 to 40 mm Hg lower than in the cortex. If this hemodynamic change occured, medullary oxygen tension may lower than normal and lead to medulla ischaemia.[12]

Oxidative Stress

The ascending loop of Henle has increased energy consumption due to contrast agents because these are osmotic diuresis inducers. The administration of contrast agents also decreases medullary oxygenation and increases medullary oxygen consumption, it has highly consequence to hypoxia injury.[13] Medullary hypoxia result in the formation of ROS (Reactive Oxygen Species) which is lead to direct tubular and endhotelial injury. This can cause endothelial dysfunction and dysregulation of tubular transport. The superoxide anions react with NO (Nitric Oxide) to produce peroxinitrate anion which is more noxious to endothelial cells. Nitric Oxide is known to be vasodilator, the reaction of ROS with NO will cause the depletion of NO itself.[13, 14]

Direct Tubular Cell Toxicity

ICM also has direct cytotoxic effect to tubular and endothelial cell which is lead to apoptosis and cell death. The direct taken up of ICM to tubular cell result in apoptosis to tubular cell and stasis of contrast in the tubule. The high concentration of ICM in the tubules brings the persistent toxicity of surrounding tubular cells.[15]

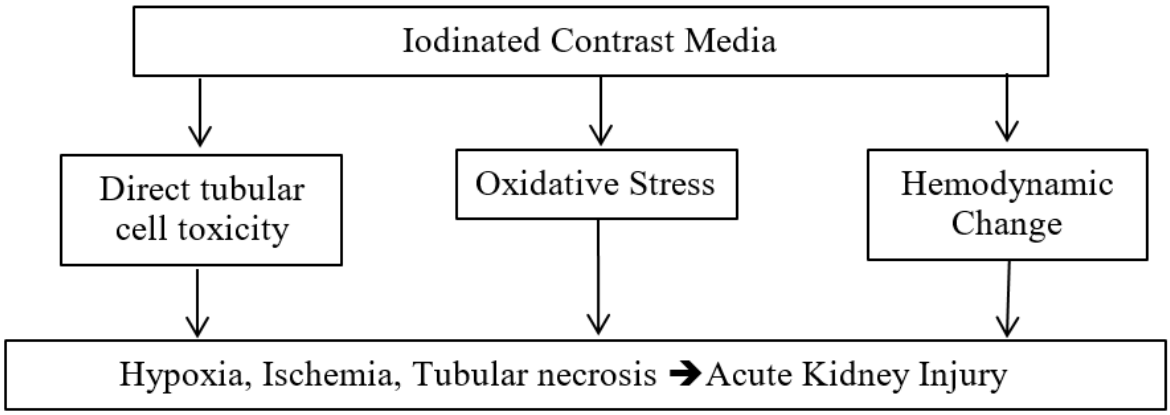

Figure 1: Pathophysiology of Renal Toxicity Related to The Administration of Iodinated Contrast Media (ICM)

Diagnosis of CI-AKI

The diagnosis of AKI is made by following KDIGO (Kidney Disease Improving Global Outcome) criteria, if one of the criteria below is appeared on the patient within 48 hours after ICM administration.[2]

1) Absolute serum creatinine increase ≥ 0.3 mg/dL (> 26.4 μmol/L).

2) A percentage increase in serum creatinine ≥ 50 % (≥ 1.5-fold above baseline).

3) Urine output reduced to ≤ 0.5 mL/kg/hour for at least 6 hours.

For CI-AKI the sign and symptom which is found above should not be attributable to any other identifiable cause of kidney failure. After the elevation of SCr level, there is typically a gradual decline at 3 to 7 days. For almost all patients with CI-AKI, the increase in SCr is within the first 24 hours; in patients with serious renal impairment, virtually all will have an increase in SCr within 24 hours. Any delay in SCr elevation results in lower detection rates of CI-AKI.[16]

Prevention

To avoid CI-AKI for the patient, doing an administration of ICM only when clinically necessary. Thus, there are several ways should be done by physician before administer ICM for both diagnostic or therapeutic procedure.

Patient Selection

Screening the risk factors of CI-AKI for the patient is important. For those with risk factors, creatinin serum can be easily measured to evaluate renal function. Creatinin serum can be used to calculate eGFR. The risks for CI-AKI is clinically important below an eGFR 60 ml/min, so it is often used as cutoff for when physicians must be consulted. Newer evidence suggest that if the eGFR below 45 ml/min, physicians must consider the necessity of ICM administration and its possible alternatives.[17] Multiple risk assessment has been developed to determine the administration of contrast media. Mehran et. al., created risk score to predict CI-AKI after coronary intervention. The higher the risk score, the greater possibility of CI-AKI to the patient.[18]

Table 2: Mehran Risk Score for CI-AKI

Risk Factors	Score
Hypotension (SBP < 80mmHg)	5
Intra-aortic Balloon pump	5
Congestive heart failure (NYHA III or IV)	5
Age > 75 years	5
Anemia (Ht < 39% in man ; < 36% in woman)	5
Diabetes	5
Volume of injected contrast media	1 for each 100 ml
Serum creatinine concentration > 1.5 mg/dl or eGFR < 60 ml/min/1.73m^2	4 2 if eGFR = 40 - 60 4 if eGFR = 20 - 40 6 if eGFR < 20

	Risk Score	Risk of Contrast induced Nephropathy	Risk of Dialysis
Low	≤ 5	7.5 %	0.04 %
Moderate	6-10	14 %	0.12 %
High	11-15	26.1 %	1.09 %
Very High	≥ 16	57.3 %	12.6 %

Contrast Selection

Choosing the correct contrast agents is also important to avoid CI-AKI. There few consideration to determine the correct contrast agent for patient. (1) Type : Type of ICM should be chosen based on osmolality and ionicity of contrast media. Osmolality of ICM compared to plasma is crucial to the risk of nephrotoxicity. Contrast media usually greater viscosity and osmolality (molecules per kilogram of water) than plasma. Ionicity is characteristic of molecule to disperse into cation and anion, leading to

more molecule per kilogram of water and increasing osmolality. Nonionic contrast media is preffered due to less osmolar than ionic contrast media. Iodine atoms of ICM influence the osmotoxic effect of contrast media: the higher the ratio to dissolve particle, the better the attenuation of x-ray.[19] Few studies demostrated that adverse side effect to contrast media range from 5 – 12 % for HOCM and 1 – 3 % for LOCM. Thus, LOCM seems to be more beneficial to the prevention of CI-AKI than HOCM.[20] Recent study of meta-analysis have found no significant difference in the rates of AKI between IOCM and LOCM.[21]

(2) Dosage: The dose of contrast agent also affects the risk of CI-AKI since it is dose-dependent to contrast media, thus the lowest possible dose decrease the risk of nephrotoxicity.[22]

* Cigarroa's formula: 5 mL of contrast per kg b.w./SCr (mg/dL) with maximum acceptable dose of 300 mL for diagnostic coronary arteriography.[23]

* Laskey's formula: volume of contrast to calculated creatinine clearance ratio with a cut-off point of the ratio at 3,7 for PCI; a ratio > 3,7 would be associated, following contrast use, with a decrease in CrCl.[24] Recently Gurm et. al. have suggested a cutoff point at 2.0: below a ratio of 2,0 AKI would be a rare complication of PCI, but it would increase dramatically at a ratio of 3,0.[25]

* A new formula seems to be superior and consists of a ratio of grams of iodine to the eGFR; a ratio of 1,42, or even better a ratio of 1,0, would prevent contrast-induced AKI.[26]

(3) Route of administration : Intravenous administration has known to be less risky than intra-arterial contrast media. Few studies demonstrated that intra-arterial ICM administration is more nephrotoxic because of the higher acute intrarenal concentration. In aortography procedure, the closer ICM injection to renal arteries, the higher risk of CI-AKI.[22]

Avoidance of Other Potential Nephrotoxic Drugs

Several drugs may also nephrotoxic to the patient such as aminoglycosides, vancomycin, amphotericin B, metformin, and NSAID. These drugs should be discontinued for patients who obtain contrast agents. Metformin (as an oral antihyperglicemic drug) has to be known that stimulates intestinal production of lactic acid, which may cause severe lactic asidosis in AKI condition. Metformin should be discontinued 12 hours before the administration of contrast agents and can be given 36 hours after the procedure.[27]

ICM are pharmaceutical agents that used for diagnostic and therapeutic procedure. Avoidance of using other nephrotoxic drug may decrease the risk of CI-AKI. Following drugs should be discontinued to prevent renal toxicity effect: aminoglycosides (have a direct nephrotoxic effect), cyclosporin A (direct cellular toxin that may disrupt lysosome function in tubules and stimulate tubulo-interstitial alterations), amphotericin (causes dystal tubule dysfunction), NSAID (reduce the synthesis of endogenous vasodilator prostaglandin, which will increase the renal toxicity of ICM).[27]

Management

Fluid Management

Administration of fluids is key to prevent the risk of CI-AKI. IV infusion of 0.9 % saline at an infusion rate of 1 mL/kg BW/hour should begin 6 – 12 hours before the injection of the contrast drug and continue for up to 12 – 24 hours after the injection. The rationale for hydration causes expansion of intravascular volume, then depress the renin-angiotensin cascade and reducing renal vasoconstriction and hypoperfusion; the result is an increase of diuresis, thus limiting the duration of contrast material contact with renal tubules and its toxicity on tubular epithelium.[28]

Other studies have found better results with the use of sodium bicarbonate rather than sodium chloride. A procedure would be administration of a bolus of 3 mL/kg BW/ hour for 1 hour of a solution of sodium bicarbonate 154 mEq/L before the injection of contrast drug, followed by 1 mL/kg/hour for 6 hours. However, others have disagreed, since no better benefit with sodium bicarbonate rather than sodium chloride.[29]

Medication

1. N-Acetylsistein

Important role for ROS has been involved in renal toxicity caused by contrast agents. Thus, antioxidant is suggested to be useful for CI-AKI. NAC has characteristic to free radical-scavanger and vasodilating effect of nitric oxide. NAC may be given as an oral dose of 600 mg twice daily (day before and day of the procedure) or an IV dose of 150 mg/kg half an hour before the procedure or 50 mg/kg administered for 4 hours.[30]

2. Statin

Patti et. al. demonstrated that a short-term high dose of atorvastatin (80 mg, 12 hours before intervention followed by a further 40 mg preprocedure dose) decreased the incidence of CI-AKI in patients undergoing percutaneous coronary interventions. Mechanism that can explain this trials is statins decrease the vasoconstricting response to angiotensin and the synthesis of endothelin, thereby preventing renal hypoperfusion and medullary hypoxia. Furthermore, contrast agents have to be known in increasing the incidence of inflammation, with formation of ROS and proinflammatory cytokines, and complement activation, which is lead to tubular obstruction. Statins have pleiotropic effects: antioxidative, anti-inflammatory, antithrombotic and reduce endothelin secretion.[31]

3. Furosemide

Furosemide has an effect of reducing active tubular reabsorption and increasing urine output, in order to decrease the duration of contrast agent's nephrotoxic effect with tubular epithelium. To prevent salt depletion, adequate fluid replacement should be given.[32] However, Solomon et. al. reported, there was an exacerbation of renal dysfunction when the loop diuretic furosemide was used in addition to IV saline solution. Therefore, the usage of furosemide as prevention of nephrotoxic effect remains controversy.[33]

4. Nebivolol

A β1-adrenergic receptor antagonist, nebivolol (5 mg/day for 1 week or 5 mg every 24 hours for 4 days) has been proven in patients with renal dysfunction undergoing coronary angiography to protect against CI-AKI, possibly acting via its antioxidant properties and NO-mediated vasodilating action.[34]

Hemodialysis

Different types of hemodialysis may remove contrast drugs from the blood in patient with chronic kidney disease. High-flux hemodialysis and hemodiafiltration remove contrast more effectively than low-flux hemodialysis or hemofiltration.[35] However, prophylactic hemodialysis in patients with reduced renal function does not diminish the incidence of CI-AKI.[36]

Conclusion

CIN or CI-AKI is defined as sudden deterioration of renal function which is caused by administration of contrast media, that cannot be attributable by other sources. Contrast agent cause the elevation of renal vascular resistance, decreasing of renal blood flow, and decreasing of GFR. Contrast agent has direct cytotoxic effect to tubular and endothelial cell which is lead to apoptosis and cell death. Contrast agent also decreases medullary oxygenation and increases medullary oxygen consumption, it has highly consequence to medullary hypoxia. Medullary hypoxia result in the formation of ROS (Reactive Oxygen Species) which is lead to direct tubular and endhotelial injury. Selecting the right contrast type, dose and route of administration, screening patient's risk factor using Mehran risk score and avoiding nephrotoxic drug are important to prevent CI-AKI. Medications such as N-acetylcysteine, statins, furosemide and nebivolol can be used to manage CI-AKI in addition to fluid administration and hemodialysis.

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