Practicing safe use of nonionic, low-osmolarity iodinated contrast

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Iodinated contrast agents have been used for many decades and play an important part in diagnostic and interventional procedures. Contrast media are generally safe, but allergy-like reactions to contrast can potentially become life threatening. To prevent adverse consequences, careful review of the patient's history for medical necessity of contrast agent is needed. This article describes the epidemiology and types of contrast reactions, factors associated with aderse reactions, premedication to prevent adverse reactions, contrast-induced acute kidney injury, contrast use among pregnant and breast-feeding patients, and contrast extravasation management.

Iodinated contrast agents were developed in the 1920s.[1,2] Starting as ionic, high osmolar contrast material (HOCM), contrast agents underwent further refinement during the 1960s with the introduction of nonionic compounds. Nonionic compounds do not dissociate in water; therefore, they are lower in osmolality. Low osmolar contrast media (LOCM) have undergone further evolution with increased hydroxyl groups replacing carboxyl groups for additional solubility in water. The lower osmolality and increased solubility in water lowers LOCM toxicity.[2] Formerly used HOCMs have significantly higher incidence of adverse reactions compared to modern LOCMs.[3,4,5] Usage of contrast materials has consequently increased exponentially as these agents have proven to be extremely safe with a low incidence of adverse reactions.[1,6] Efforts aimed minimizing risks of contrast reactions are essential to providing high-quality healthcare.

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Epidemiology

The incidence of allergy-like reactions to LOCMs is relatively rare, with estimates in the range of 0.2-3.1%.[1,7] Most of these are classified as mild and moderate. There is increased incidence of adverse reactions among younger patients, which may be due to psychological effects.[8]

Risk factors exist that predispose patients to contrast reactions. Prior history of allergy to contrast increases the subsequent risk of reaction up to fivefold. Allergies to other medications, foods and environmental allergens also increase the risk; however, the magnitude of increased risk is unclear. Asthma and cardiovascular disease are also known risk factors for contrast reaction.[5,6,9,10]

Anxiety has been shown to increase the likelihood of contrast reaction. Advising patients of the side effects they may experience may help to minimize anxiety, and thereby reduce the risk of adverse reaction.[8,11] Administering anxiolytics before contrast injection to reduce contrast reaction is not routinely practiced.

Controversy exists regarding the association of beta-blockers and adverse contrast reactions. Despite the lack of consensus on beta-blocker as a risk factor, studies indicate decreased efficacy of medications to treat contrast reactions if they occur.[12,13]

Nature of contrast reactions

Contrast reactions are not true allergic reactions. Symptoms such as urticaria and anaphylactoid reactions do not stem from true allergic reactions as one would expect after ingesting food or other immune-system-provoking substance. Examination of patients after contrast reaction has not revealed signs of antibody formation as one would expect after a true allergic reaction. Contrast agent molecules are theoretically too small to elicit antibody formation. Contrast agent reactions are therefore more properly classified as anaphylactoid reactions.[5,13,14]

Contrast reactions can be classified into 3 categories: mild, moderate and severe. Mild reactions include nausea, vomiting, limited urticaria and self-resolving vasovagal reaction. Moderate reactions include symptomatic urticaria, diffuse erythema and vasovagal reaction that responds to treatment. Severe reactions include diffuse edema, seizures and vasovagal severe bronchospasm.[5,11]

Table 1 outlines some considerations that should be taken in patients who report previous allergic reaction to IV contrast administration.

Premedication

Steroids and antihistamines are effective in minimizing adverse reactions in patients with risk factors. There are various protocols for premedication. One frequently used protocol is the Greenberger protocol, which includes

Table 1: Considerations in patients reporting allergy to contrast on previous study

- Weigh the risk versus benefit
- Check what the allergic reaction was
- Look for an alternative — MRI, US, VQ scan
- If study is needed, premedicate

Table 2: Patients who may require creatinine check prior to IV contrast administration

- Age > 60
- History of renal disease, including:
  - Dialysis
  - Contrast-induced nephrotoxicity
  - Kidney transplant
    - Single kidney
    - Renal cancer
    - Renal surgery
- History of hypertension requiring medical therapy
- History of diabetes mellitus
- Metformin or metformin-containing drug combinations

prednisone 50mg at 13, 7, and 1 hr, and diphenhydramine 50mg at 1 hr prior to contrast injection.[15,16,17] In settings where emergent contrast injection is required, higher doses of intravascular steroids can be used. As an example, methylprednisolone IV 40mg every 4 hrs and diphenhydramine IV 1 hr before contrast administration may be followed. As with any medication, steroids have side effects of their own; therefore, careful consideration of the risks versus benefits should be performed prior to administration.[9,18,19]

Seafood and drug allergies

Allergies to shellfish have long been mistakenly correlated with iodinated contrast agent allergy. There is no evidence regarding cross reactivity between shellfish allergy and anaphylactoid reaction to contrast. The previously held notion that patients with a history of seafood allergies are at increased risk for adverse reaction to contrast is no longer valid.[9,14,20] A strong history of multiple drug allergies should increase awareness of the possible risk of a reaction, but there is no need to avoid injection of contrast media unless the allergy is to the IV contrast itself.[5,21]

Asthma and diabetes

A history of asthma has been thought to be a good predictor of increased risk; risk may be higher in patients with active asthma and/or bronchospasm. An inhaler should always be available when contrast media are being administered.[21,22] Diabetic patients on metformin with normal renal function at baseline but with other comorbidities, such as liver or cardiac dysfunction, should stop metformin before receiving contrast and may resume 48 hrs afterwards if patient has no other intercurrent risk factors for renal damage. Patients with renal insufficiency should stop metformin and have repeat lab tests for return to baseline renal function or show signs of clinical stability prior to restarting metformin.[23] Metformin does not need to be stopped prior to contrast administration in patients with normal renal function and without other comorbidities.[11,24] Stopping metformin and/or rechecking creatinine levels 48 hours after the procedure may be unnecessary, because the risk of contrast-induced nephropathy in patients with normal renal function without other comorbidities is very low.

Observing patients for contrast reactions

Most adverse reactions occur within 5 minutes of contrast administration. Contrast is usually given through the intravascular route, which results in a rapid appearance of reactions. Contrast administered through the alimentary tract and intracavitary spaces can also cause adverse reactions, as some contrast is absorbed. Patients with moderate to severe contrast reactions should be observed until they demonstrate clinical stability.[9,16]

Creatinine check prior to IV contrast

Not all patients require measurement of serum creatinine before receiving contrast, as individuals most at risk for contrast-induced acute kidney injury have a history of renal insufficiency.[21] A recent study showed that patients with stable baseline serum creatinine of < 1.5 mg/dL are not at risk for renal injury following contrast administration.[25] The general consensus is to allow contrast use in patients with creatinine ≤ 1.5 mg/dL, exercise caution in patients with creatinine in the range of 1.6 - 2.0 mg/dL, and to avoid contrast in patients with creatinine > 2.0 mg/dL. Table 2 lists risk factors for which the American College of Radiology recommends practicing caution in administering IV contrast.[11]

Creatinine cutoff for administering IV contrast

Elevated serum creatinine levels indicate poor renal function.[26-28] Rising creatinine levels indicate that an insult to the kidney has occurred, with the elevation in creatinine lagging behind that of renal damage by 24-72 hrs. Among patients with compromised renal function and elevated creatinine, the correlation

Table 3: Contrast use in dialysis patients

- Most patients can wait until their next regularly scheduled dialysis
- History of severe underlying cardiac disease and the small osmotic load of contrast will potentially send patient into pulmonary edema; urgent dialysis may be indicated
- Theoretical risk of making an oliguric patient anuric

between acute renal damage and rise in creatinine becomes less clear. Recent studies suggest that acute renal injury as indicated by elevation in serum creatinine level seen after a contrast CT examination may not be due to the contrast material. Instead, the injury may be due to other confounding variables.[29,30] Therefore, setting an absolute creatinine cutoff value for administering intravenous contrast is difficult. Creatinine cutoff of 2.0 mg/dL is probably safe for most patients with stable chronic renal insufficiency.[11,31]

Contrast-induced acute kidney injury

Contrast-induced acute kidney injury refers to the sudden decrease in renal function following contrast administration in the absence of other nephrotoxic agents. Although no formal criteria exist, a general guideline is elevation of serum creatinine by ≥0.5 mg/dL or ≥25% occurring within 48 hrs after contrast administration, and the absence of an alternative etiology.[13,16,31,32] Serum creatinine is not a reliable marker for renal function, as values depend strongly on age, gender, muscle mass and nutritional state.[33] A more accurate measurement is the glomerular filtration rate.[11,34]

A recent study showed that using an estimated glomerular filtration rate cutoff of 45 mL/min/1.73 m^2 identified small but significantly more patients at risk of contrast induced acute kidney injury after contrast administration as well as patients at low risk who may be misclassified as being at risk for acute kidney injury when using the method of serum creatinine cutoff of 1.5 mg/dL.[35]

Prevention of contrast-induced acute kidney injury consists mainly of withholding contrast whenever possible and maximizing hydration with IV crystalline solution.[10,23,36,37] Among patients undergoing cardiac catheterization, left ventricular end-diastolic pressure-guided fluid administration was useful in preventing renal injury.[38] Controversy exists with regard to the usefulness of other medications to prevent acute kidney injury, such as sodium bicarbonate, N-acetylcysteine, fenoldopam, and theophylline.[23] Studies show N-acetylcysteine decreases serum creatinine; however, there is no protection against renal failure.[11,39,40]

A recent study questions the widely held belief that contrast induces acute renal injury in patients with chronic renal insufficiency. The study concluded that no significant relationship exists between contrast administration and acute renal injury.[29] Another study concluded no significant increased rates of acute renal injury after LOCM administration among critically ill patients.[41] How much the impact of these results will change the practice of exercising caution in administering contrast to patients with decreased renal function remains to be seen.

Dialysis, pregnant and breast-feeding patients

Patients with chronic kidney disease on dialysis may receive contrast. There is a theoretical risk of causing an oliguric patient anuric. For anuric patients, risks include causing fluid overload and pulmonary edema. Emergent dialysis is not needed unless patient shows signs of cardiopulmonary decompensation.[11,42] Table 3 lists factors that need to be considered in a dialysis patient.

Iodinated contrast agents cross the placenta; therefore, the fetus will be exposed to small amounts of contrast. A limited number of studies show no evidence of mutagenic or teratogenic potential of contrast material. Association with hypothyroidism has not been shown in fetuses exposed to iodinated contrast.[13,43,44]

Very small amounts of contrast are excreted into breast milk. The amount of contrast that a baby will ingest and absorb through the gastrointestinal tract is far less than that allowed for radiological examinations among infants. There is no need for mothers to discontinue breast-feeding after receiving contrast material. If the mother is very concerned about the unknown effects of contrast on her baby, she may express and discard her breast milk for 24 hrs after her examination. Virtually no contrast remains within the mother after 24 hrs.[11,45]

Extravasation

Two main complications that can occur after contrast extravasation are skin necrosis and compartment syndrome. Extravasation into the soft tissues can cause necrosis of the surrounding skin as contrast elicits a foreign-body response and creates significant inflammation. Extravasation of relatively large amounts of contrast within a small volume of space such as the wrist or hand increases the risk for compartment syndrome.[11,46-48]

Conservative treatment includes application of cold or warm compresses, elevation of the affected extremity with serial pulse and sensation exams, and local massage.[47] Cold compresses are thought to relieve pain and decrease inflammation. Warm compression is thought to increase blood flow to the area of extravasation and promote absorption of contrast. Patients should be monitored for several hours to make sure no further complications develop.[11]

Surgical consultation for management of contrast extravasation depends on patient's symptoms. Previously, greater than 100 mL of extravasation was used as guideline for obtaining consultation. However, the most recent recommendation is to monitor for symptoms, such as increasing pain, skin necrosis and paresthesia in the affected limb, and decreased capillary refill.[11,49,50]

Conclusion

Careful consideration of contrast reactions and contrast-induced nephrotoxicity among select patients will minimize complications related to contrast use. Use of iodinated contrast agents as part of radiologic examination is safe among most patient populations, including pregnant patients and breast-feeding mothers, and should be utilized when medically necessary.

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