International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Radiographic Contrast Media: An Introduction, Effects on Intravascular Administration, Severity of Reactions and its Management

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Abstract: ***Diagnostic imaging relies heavily on intravascular radiographic contrast agents, such as CT scans, ultrasounds, and MRIs, to enhance the visibility of internal organs and structures. helps distinguish tissues from their surroundings, revealing blood vessels, organ flow, and gastrointestinal, biliary, or urinary tract interiors. However, these agents can also have serious side effects, including minor, intermediate, and severe life - threatening reactions. The risk of adverse reactions is low, but there is a small probability of mild to fatal reactions with every administration. LOCM non - ionic have a lower osmolality than blood, reducing the occurrence of adverse reactions than HOCM. The severity of reactions varies from mild to severe. Contrast Induced Nephropathy (CIN) is a common side effect characterized by impairment or acute renal failure within 48 - 72 hours of administration. An individual's highest risk category for developing CIN is thought to be those with moderate - to - severe chronic renal disease. The Greenberger preparation is a premedication strategy for at - risk patients. Magnetic resonance imaging contrast agents, such as gadolinium chelates, are commonly used to enhance contrast between normal and diseased tissues due to their paramagnetic effect. NSF is a rare and potentially severe systemic disease characterized by fibrosis of the skin, joints, eyes, connective tissues, and internal organs.***

Keywords: Contrast Induced Nephropathy, Gadolinium, Chelates, Nephrogenic Systemic Fibrosis

1. Introduction

Intravascular radiographic contrast chemicals serve an important role in diagnostic imaging by improving the visibility of interior organs and structures using imaging methods. Contrast medium is used for CT scans, *ultrasounds, and MRI. Since the beginning of CT scanning, intravenously administered iodinated contrast media have been utilized to improve the visualization of normal and pathological structures. Structures appear denser and more apparent due to x - ray attenuation. Water soluble contrast media tri - iodobenzoic acid derivative was introduced in 1950 into the clinical radiology. Helps to distinguish one tissue or structure from its surroundings that show the blood vessels, blood flow in organs, interior of the gastrointestinal, biliary, or urinary tract. Iodine based contrast media are usually classified as monomer and dimer. They are useful for improving imaging investigations, but they can also have serious, potentially fatal side effects. Acute responses or adverse effects to contrast media can be classified as mild, intermediate, and severe life - threatening reactions. The mild reactions including flushing, queasiness, limbs pain, vomiting, headache that requires no treatment, intermediate reaction includes more serious degree of listed symptoms with moderate hypotension. Life - threatening reactions includes all symptoms included laryngeal oedema, pulmonary oedema, pulmonary collapse. IV contrast medium is filtered in the glomerulus, concentrated in the renal tubules and excreted in the urine. When administering iodinated contrast, extreme caution is usually advised. Within 20 minutes of injection, the majority of acute, serious adverse responses to contrast media happen. Because of this, following an injection of contrast media, the patient needs to be observed for at least twenty minutes. The phrase contrast - induced nephropathy refers to a loss in renal function caused by contrast medium. Non - ionic contrast media have reduced the number of mild and moderate contrast reactions while not changing the risk of anaphylactic reaction and mortality.

Iodinated Contrast Agents (Water Soluble)

Intravascular applications commonly employ water soluble contrast agents, which are molecules containing atoms of iodine. There is a strong relationship between the osmolality, viscosity, and iodine content of contrast media. There are two types of iodinated contrast media: ionic and non - ionic. These can be low osmolality or high osmolality. As CT becomes more commonly utilised, the number of patients that are exposed to iodinated contrast agents grows. Fortunately, the risk of an adverse response is low; but, regardless of dosage or delivery mechanism, there is a slight chance of a moderate to deadly reaction with every contrast agent administration. Water soluble contrast media is divided into two on the basis of osmolality, the high osmolar contrast media (HOCM) and low osmolar contrast media (LOCM). Osmolality rises with an increase in adverse effects. Adverse effects cannot be independently predicted by the iodine content. The adverse

reactions caused by hyperosmolality of the contrast media includes - erythrocyte damage, endothelial damage, blood brain barrier damage, hypervolaemia and cardiac depression. Non - ionic dimers are preferable because they have a lower osmolality and less chemotoxicity. They cost more, though, and have a higher viscosity than non - ionic monomers. High osmolar ionic agents have been replaced with low osmolar ones due to safety concerns.

High osmolar contrast media / Ionic monomers - For over decades, ionic contrast agents, also known as high osmolality contrast media, have been regarded as both safe and effective. All iodinated contrast agents are made up of a benzene ring with three iodine atoms. Acid salts known as ionic media split into positively charged cations (such as sodium and meglumine) and negatively charged anion (such as diatrizoate and iothalamate) that contain iodine in water. Ionic agents have osmolality 5 - 8 times greater than plasma. Significant hemodynamic, cardiac, and subjective effects such as vasodilation, heat, and pain are brought on by high osmolality and viscosity. Contrast media are rapidly released into the extracellular space after an IV infusion. Renal glomerular filtration is used for excretion. Vicarious excretion via the intestines and liver happens when renal function is impaired.

Low osmolar contrast media - The osmolality of non - ionic contrast materials, also known as low osmolality contrast media, is lowered to one to three times that of blood, which significantly lowers the already low occurrence of adverse responses. There are 3 types of low osmolality contrast media: (i) non - ionic monomers, (ii) ionic dimers, and (iii) non - ionic dimers. The triiodinated benzene ring in non - ionic monomers is soluble in water due to the hydroxyl groups added to the organic side chains at positions 1, 3, and 5. Lacking a carboxyl group, it does not ionize in solution, having iodine particle ratio is 3: 1. Ionic dimers are formed by joining 2 ionic monomers and eliminating 1 carboxyl group, so known as monoacid dimers, having iodine particle ratio is 6: 2. Ex – ioxaglate. Non - ionic dimers formed by 2 joined non - ionic monomers so iodine particle ratio is 6: 1. Examples of non - ionic dimers are iotrol, iotrolan (isovist), iodixanol (visipaque).

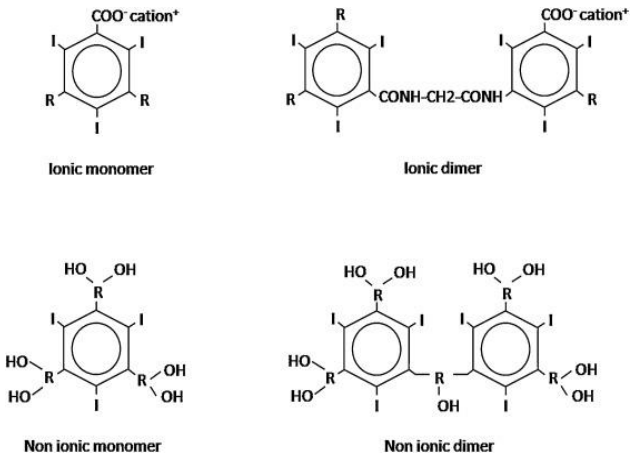

Figure 1: Chemical structures of contrast media

Table 1: Commonly used contrast agents

Name	Type	Iodine Content (mg/mL)	Osmolality
IONIC			
Diatrizoic acid (Hypaque 50 GE Healthcare) Urograffin	Monomer	300	1550 (high)
Metrizoate isopaque (Coronar 370; Nycomed A/S)	Monomer	370	2100 (high)
Ioxaglate (Hexabrix)	Dimer	320	580 (low)
Conray (Iothalamate)		280	1400 (high)
NONIONIC			
Iopamidol (Isovue 370; Bracco Diagnostics Inc.)	Monomer	370	796 (low)
Ioversol (Optiray)	Monomer	320	702 (low)
Iohexol (Omnipaque 350; GE Healthcare)	Monomer	350	884 (low)
Iopromide (Ultravist; Bayer Healthcare)	Monomer	300	
Iodixanol (Visipaque 320; GE Healthcare)	Dimer	320	290 (iso)

The undesired effect that occurs following the administration of contrast media is defined as an adverse reaction to agents. Although it is impossible to forecast a contrast reaction with accuracy, people who have previously experienced a contrast reaction, asthma attack, or allergy are obviously more vulnerable. Patients with heart problems have cardiovascular side effects more frequently and with greater severity. Severity of reactions are mild, moderate, severe and death.

Mild reactions - The majority of side effects are mild. Because ionic contrast agents have a higher osmolality, they are more likely to cause nausea, vomiting, rash, light headache, warmth at the injection site, and discomfort at the injection site. Treatment is usually not necessary for these reactions. For a duration of twenty to thirty minutes, patients should be monitored to make sure the reaction doesn't get worse.

Moderate reactions - Although moderate reactions don't pose a threat to life, their symptoms frequently need to be treated. Patients who experience modest laryngeal edema, urticaria, bronchospasm, hypotension, severe hives, or vasovagal responses should be closely watched until their symptoms go away. Hives with symptoms can be effectively relieved with diphenhydramine. For bronchospasm, beta agonist inhalers are helpful, while for laryngeal spasm, epinephrine is recommended. Hypotension and vasovagal responses should be treated with leg elevation.

Severe reactions - severe which are life - threatening and always require medical intervention. It includes arrhythmias, overt bronchospasm, laryngeal edema, pulmonary edema, seizure, severe angima or coma and death.

Contrast Induced Nephropathy (CIN) Acute renal failure or impairment that occurs 48–72 hours after intravenous contrast administration is the most common definition of Contrast Induced Nephropathy (CIN). Serum creatinine levels rise in the first 24 hours after contrast administration, peak at 3–5 days later, and typically return to baseline by 10–14 days. Permanent kidney impairment affects certain people. The primary strategy for preventing CIN is hydration treatment. Ascorbic acid, bicarbonate, N - acetylcysteine (NAC), statins,

and other treatments have also been studied as CIN treatments. Patients with pre - existing renal illness, especially those with diabetes mellitus and multiple myeloma, which can cause renal failure, are the main risk factors. Use the lowest amount of contrast material feasible for individuals who are more vulnerable, and keep a close eye on their renal function by taking serum creatinine levels before and after the radiography operation once a day for five days. The treatment of contrast - induced nephropathy is similar to that of acute renal failure resulting from other causes after it has been recognised.

Regulating common reactions

Extravasation - Injections with hands or power might cause extravasation. Extravasation is more common in the elderly, young children, newborns, individuals experiencing altered awareness, and people with underlying vascular disease. Little contrast media extravasations typically cause a slight inflammatory response in the skin but no lasting effects. Greater quantities (50–75 mL) may cause compartment syndrome or chemotoxicity - related tissue damage. Patients typically get swelling and burning at the injection site for a long time. Early care requires measuring the patient's pulse distal to the injection site and documenting any first erythema and edema. Smaller extravasations can be treated with cold compresses and elevation of affected extremity above the heart level. It is best to speak with a surgeon in cases when swelling, discomfort, and discolouration are persistent. Higher - osmolality contrast agents typically result in more severe complications from contrast extravasation.

Air embolism - An air embolism occurs when gas or air enters the circulatory system. Complications are expected to arise whenever air in IV tubing is permitted to enter the vascular system. Dyspnea, coughing, chest discomfort, pulmonary edema, hypotension, and neurologic impairment are among the symptoms. Treatment include giving the patient 100% oxygen, putting them in a left lateral decubitus position and giving them hyperbaric oxygen if necessary.

Green Berger Regimen

Premedication techniques included 50 mg of prednisone given 13 and 7 hours and 1 hour before IV contrast (total150 mg of prednisone) and 50 mg of diphenhydramine given 1 hour before IV contrast. This regimen, called the Greenberger preparation, is recommended by the American College of Radiology (ACR) guidelines on contrast media as an appropriate premedication technique for patients who are at - risk.

1) For patients with prior mild allergic reactions - premedication is recommended to reduce the risk.
2) For patients with prior moderate or severe allergic reaction - consider scanning without IV contrast or consider an alternative modality (e. g. MRI, USG).
3) Change the contrast agent to be injected - patients who have documented reaction to a specific contrast agent.

Table 2: Premedication protocols for patients with previous or increased risk of contrast agents

Premedication	Protocol for adults	Protocol for children
Corticosteroids (any of the following)	Prednisone: 50mg PO at 13, 7 and 1 hour before IV contrast	Prednisone: 0.5 - 0.7mg/kg PO (up to 50mg) at 13, 7 and 1 hour before IV contrast
	Hydrocortisone: 200mg intravenously, 1 hour before contrast injection	
	Methylprednisone: 32mg PO at 12 and 2 hours before IV contrast	
Antihistamine	Diphenhydramine (Benadryl): 50mg intravenously/orally at 1 hour before IV contrast	Diphenhydramine (Benadryl): 1.25mg/kg intravenously/orally at 1 hour before IV contrast

Guidelines for the safe application of iodinated contrast materials

1) Verify whether intravascular contrast agents are indeed required for every radiography test where the delivery of contrast is a factor.
2) For each inspection, use the least amount of contrast agent that is effective.
3) Employ a premedication regimen for individuals who are deemed to be at high risk of experiencing an adverse reaction, such as those who have a history of intravascular contrast agent adverse reactions in the past or who have a demonstrable history of allergies or asthma.
4) Determine the eGFR and measure serum creatinine levels.
5) Promote oral hydration for all patients receiving contrast agents, and for patients who are more susceptible to CIN, think about IV hydration with normal saline both before and after IV contrast treatment.
6) Pregnant women should try to avoid using contrast agents. Contrast agents penetrate the foetal circulation after crossing the placenta.

Contrast Agents Used in Magnetic Resonance Imaging

By changing the relaxation periods, contrast agents are widely employed in magnetic resonance imaging (MRI) to improve the contrast between normal and diseased tissues. The characteristic of MRI is that the signal intensity is determined by several different factors. Therefore, in order to reduce dosage and potential toxicity, the contrast agents must be able to impact these parameters at low concentrations. The gadolinium - based magnetic resonance contrast agents are especially safe and do not cause nephrotoxicity like iodinated contrast media do. The MRI contrast agents that are most frequently utilized are gadolinium chelates that are injected intravenously. Their ability to enhance tissue on MRI is due to the paramagnetic effect that the molecule's gadolinium content produces. As the body's tissue attenuates the xray beam differently in CT and x - ray scanning, this results in differences in picture contrast. However, in MRI there are some parameters that determines the MR signal intensity and contrast are spin density, magnetic susceptibility, relaxivity, diffusion and perfusion. Paramagnetic gadolinium ion complexes and superparamagnetic (iron oxide) magnetite particles make up the majority of MRI contrast agents.

Contrast agents are divided into two categories.
First, paramagnetic substances, such as gadolinium and other lanthanides, primarily decrease the longitudinal T1 relaxation characteristic, producing a stronger signal. These are low molecular weight compounds with iron, manganese, or gallium as the active ingredient. These elements all create good relaxivity contrast agents because they all contain unpaired spins in their outer shells. Gd - DTPA (gadopentetate dimeglumine), Gd - HP - DO3A (gadoteridol), and Gd - DTPA - BMA (gadodiamide) are the agents that have received FDA approval. These are quickly eliminated by glomerular filtration and serve as extracellular contrast agents.

Super - paramagnetic iron oxides (SPIO) are the second class of materials. They mostly look black on MRI and have a significant impact on the transversal T2 relaxation characteristics. T1 and T2 relaxation times are shortened by these drugs because they provide spin spin relaxation effects. The basis of crystalline iron oxide, or SPIO and ultrasmall superparamagnetic iron oxide (USPIO), often contains thousands of iron atoms.

Table 3: Contrast agents used in MRI

Name	Ionicity	Osmolality (mosm / kg H2O)
Omniscan	Non - ionic	780
Prohance	Non - ionic	630
Gadovist	Non - ionic	1603
Magnevist	Ionic	1960
Dotarem	Ionic	135
Multihance	Ionic	1970

Classification of Contrast Agents

Paramagnetic contrast agents
In the presence of paramagnetic species, spin lattice relaxation times T1 and T2 may be significantly reduced. Unpaired electrons are present in paramagnetic species. The primary issue with naturally occurring paramagnetic heavy metal ions is their toxicity. Superparamagnetic iron oxide (SPIO) based colloid is another, more recent class of paramagnetic contrast agents.

Gadolinium (III) complexes
Gadolinium (III) is distinguished by having a large number of unpaired electrons—seven. Gd3+ ions in their unbound form are quite poisonous. It is known that Gd3+ prevents Ca2+ from attaching to the sarcoplasmic reticulum of the mammalian heart. Hemodynamic disruption might be the toxicity's mechanism**.**

Monocrystalline iron oxide nanocompounds (mion)
MION compounds are a relatively young but quickly developing class of MRI contrast agents. In contrast to the single authorised compound containing gadolinium, MION (also known as SPIO) comes in many variants. Typically, the size of the particles ranges from few to several hundred nanometres.

Metalloporphyrines of iron (iii) and manganese (iii)
For many years, porphyrins have been recognised as markers of several metabolic conditions and disease states. When used as MRI contrast agents for tumour identification, they have advantageous characteristics.

Nephrogenic Systemic Fibrosis (NSF)
A recently identified condition known as nephrogenic systemic fibrosis (NSF) only affects patients who have renal failure. The development of NSF after being exposed to gadolinium - based magnetic resonance (MR) contrast agents has been linked. The hallmark of nephrogenic systemic fibrosis characterized by fibrosis of the skin, joints, eyes, connective tissues and internal organs. Skin condition characterized by thickening and hardening of the skin with fibrotic nodules and plaques. Furthermore, internal organ involvement happens, which finally results in death. NSF is a delayed response that often manifests many weeks following the patient's administration of the contrast agent. With end - stage renal disease, the average patient is middle - aged. After being exposed to gadolinium - based contrast agents, the initial symptoms of NSF may appear hours later, but they can also appear up to three months later. The illness usually starts out as subacute swelling of the distal extremities, which is followed in the following weeks by significant skin induration and, on occasion, an expansion to the lower belly, thighs, and forearms. Aggressive skin induration may be accompanied by persistent discomfort, twitchy muscles, and decreased skin suppleness. Radiography may reveal soft tissue calcification. Four FDA - approved gadolinium contrast agents—Omniscan, Multihance, Magenevist, and Optimark—have been mostly linked to NSF. Currently it is thought that patients with an estimated glomerular filtration rate of less than 30 should not receive gadolinium - containing contrast.

2. Conclusion

On the daily basis radiological practices and procedures iodinated and gadolinium - based contrast media is well known to be used widely for the good opacification. The use non - ionic monomer has somehow reduced the number of contrast reactions with decrease in osmolality over ionic contrast media. Contrast induced nephropathy is the risk for patients with pre - existing renal disease. It is not suggested to use gadolinium instead of iodinated contrast medium in order to reduce the risk of nephrotoxicity. Initial treatment and drugs should be kept ready after the contrast media injected intravenously whether it is used for X - ray or MRI studies.

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