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The Impact of Contrast Media on Image Quality in MRI: Simple Review Article

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Abstract

Contrast media (CM) are employed in imaging modalities to amplify the distinctions between bodily tissues in pictures. An optimal contrast agent should attain a remarkably high level of concentration in the tissues while avoiding any detrimental consequences. Regrettably, doing this has thus far proven unattainable, and all current CM options have negative consequences. The growing utilization of CM is expected to result in various challenges, such as ensuring compliance and appropriateness of CM usage, selecting the most suitable contrast agent, addressing off-label use, assessing specific patient populations, and possessing the necessary skills to handle emergency situations that may arise after CM administration. An even more significant and potentially crucial matter is the issue of informed consent. This entails the responsibility to provide patients awaiting the administration of CM with detailed information about the procedure itself, any alternative procedures available, the extent of the risks associated with using CM, and the risks associated with refusing the procedure. This review mainly discusses image quality in MRI, MRI contrast agents complexes, and effect on image.

Keywords: Contrast media, CT, MRI, contrast agent, image, radiology

Introduction:

Contrast agents are frequently employed in medical imaging to amplify the distinctions between structures or fluids within bodily tissues. They can be employed in radiological techniques such as radiography, fluoroscopy, angiography, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound. Each technique utilizes different types of contrast media, which are selected based on the chemical and physical properties of the agents. There is no such thing as an optimum contrast medium [1].
It should be feasible to administer the optimal agent rapidly or consume it orally. The substance should promptly exit the body, once it has improved the relevant structures, without altering its composition or generating any detrimental effects or bad reactions. The majority of agents elicit discomfort and unpleasant reactions to varying extents. Common symptoms include discomfort such as a metallic taste and/or a sensation of warmth. Severe responses necessitating medical intervention are rare. The initial non-renal adverse reactions are consistent across all forms of contrast media. However, there are variations in terms of acute renal adverse reactions, late reactions, and very late reactions [1-3].
The majority of the agents are eliminated from the body within 24 hours provided that the patient's renal function is normal. If the patient has significantly impaired renal function, it may take several weeks for the

drug to be eliminated from the body. Iron-based agents, similar to other iron ions, are introduced into the natural circulation. Hepatobiliary gadolinium-based drugs are eliminated to some extent through the hepatobiliary system, while manganese ions are exclusively excreted by the liver. Barium products and iodine-based oral medications remain within the gastrointestinal tract without being broken down [1-3].

The most effective utilization of contrast will vary based on the specific modality and physics of the imaging device. Radiographs and CT scans demonstrate the attenuation of an energy signal as it traverses a target tissue. Both the energy beam's and the target's physical qualities are variables that contribute to the signal loss. To maximize intrinsic contrast, one can modify the wavelength, amplitude, and frequency of the beam. Diverse methodologies are employed to differentiate between a rib fracture and pneumonia, despite both investigations include the same anatomical areas. The lung parenchyma differs from bones in terms of its physical density, atomic structure, and location. Although it is possible to alter the approach to enhance certain properties of the tissue, the system may not be able to accurately detect the pathology or tissue of interest until external variables are introduced. The substance used to highlight or enhance these otherwise inconspicuous findings is known as contrast media [4,5].

A systematic review including 17 papers was conducted in 2018 on contrast media extravasation to find factors related to higher extravasation risk found that contrast media extravasation is uncommon but roughly 6 times less prevalent with gadolinium-based contrast agents (GBCA) for MRI compared with iodinated contrast utilized in CT [6].

Understanding Image Quality in MRI:

MRI contrast agents are commonly employed to enhance the contrast disparity between healthy and diseased tissues. In 1981, a clinical MRI research was conducted utilizing ferric chloride as a contrast agent in the gastrointestinal (GI) tract, marking the first instance of contrast-enhanced human MRI following the advent of clinical MRI. In 1984, Carr et al. initially demonstrated the efficacy of a gadolinium compound as a contrast agent for intravascular MRI diagnostics. Currently, about 50% of MRI investigations conducted are those that involve the use of contrast agents, and this is an increasing phenomenon. Ongoing research is continuously uncovering and examining more advanced contrast agents. The safety of contrast agents for clinical usage is subject to rigorous evaluation. This review tries to categorize the MRI contrast agents identified thus far into appropriate groups and to describe their uses, structures, modes of action, pharmacokinetics, and pharmacodynamics [7-9].

MRI contrast agents can be classified based on several characteristics, including magnetic properties, chemical composition, presence or absence of metal atoms, route of administration, impact on the magnetic resonance picture, biodistribution, and application [9].

Most MRI contrast agents consist of either paramagnetic gadolinium ion complexes or superparamagnetic magnetite particles composed of iron oxide. Paramagnetic contrast agents are often composed of dysprosium (Dy^{3+}), gadolinium (Gd^{3+}), or manganese (Mn^{2+}), which are lanthanide and transition metals, respectively. These agents are characterized by their ability to dissolve in water [7,10].

Gadolinium (III) is the most frequently chosen metal atom for MRI contrast agents because to its high magnetic moment and exceptional stability, characterized by the presence of unpaired electrons. These contrast agents have paramagnetic properties because they contain unpaired electrons. Specifically, gadolinium has seven unpaired electrons, dysprosium has four unpaired electrons, and manganese has five unpaired electrons. Gadolinium-based contrast agents reduce the T1 and T2 relaxation period of nearby water protons. These effects enhance the signal intensity of T1-weighted pictures, while diminishing the signal intensity of T2-weighted images. T1 shortening is shown at lower concentrations of gadolinium, while T2 shortening occurs at greater concentrations. However, the clinical utility of T2 shortening is limited due to the higher risk of toxicity. Thus, in traditional clinical practice, T1 is assessed following the delivery of extracellular drugs. Transition metal ions, such as high spin manganese (II) and superparamagnetic iron oxide like iron (III) oxides, have a significant impact on T2 relaxation [10-12].

Gadolinium-based contrast agents: Exhibiting paramagnetism:

Gadolinium (III)-based contrast agents are classed into three groups: extracellular fluid (ECF) agents, blood pool contrast agents (BPCAs) and organ-specific agents [7].

Contrast agents that are manganese-based: Exhibiting paramagnetism:

In the form of manganese chelates or manganese-based nanoparticles, manganese serves as a contrast agent. Manganese chelates, such as manganese dipyridoxyl diphosphate (Mn-DPDP), significantly increase the T1

signal intensity and have been utilized for the detection of liver lesions. Within the human body, the chelate undergoes dissociation, resulting in the separation of manganese and DPDP. Manganese is absorbed by hepatocytes and eliminated by the biliary system, while the DPDP compound is expelled by the renal system. The level of detail in research on Mn-based nanoparticles is somewhat lower compared to extensively investigated nanoparticles based on iron oxide [13].

Manganese-enhanced MRI (MEMRI) employs manganese ions (Mn^{2+}) as a contrast agent, which finds utility in animal experimentation. Manganese ions (Mn^{2+}) are able to permeate cells via utilizing calcium (Ca^{2+}) channels. Consequently, this particular category of contrast agents can be employed for the purpose of functional brain imaging. Prior research utilizing MRI has indicated that Mn^{2+} carbon nanostructure complexes, specifically those composed of graphene oxide nanoplatelets and graphene oxide nanoribbons, have exceptional efficacy as contrast agents for MRI [14].

Iron oxide contrast agents are superparamagnetic:

There exist two categories of iron oxide contrast agents: superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO).

Superparamagnetic contrast agents are composed of iron oxide nanoparticles that are dispersed in colloidal form. When used in imaging, they attenuate the T2 signals in the tissues that absorb the contrast agent, resulting in a decrease in intensity. SPIO and USPIO have demonstrated favorable results in diagnosing liver cancers in certain instances. SPIO, launched as a liver contrast agent twenty years ago, was the pioneering nanoparticulate MRI contrast agent. It continues to be utilized for clinical imaging purposes. SPIOs (superparamagnetic iron oxide nanoparticles) and USPIOs (ultrasmall superparamagnetic iron oxide nanoparticles) such Feridex I.V., Resovist, Sinerem, and Clariscan have received approval for previous usage.

Nevertheless, with the exception of the oral iron oxide contrast agent Lumirem/GastroMARK, these agents are presently not accessible [14].

The contrast materials in this group possess nano-sized dimensions and unique particle morphologies, enabling distinct biodistribution and uses that are not observed with conventional contrast agents. Currently, nanoparticulate iron oxide is a widely utilized and distinctive agent in clinical practice. Due to the advanced molecular and cellular imaging technologies, disease-specific biomarkers may now be visualized at microscopic and molecular levels. As a result, additional nanoparticles have gained significant interest as possible MRI contrast agents.

Thanks to significant advancements in nanotechnology, innovative nanoparticulate MRI contrast agents have been created, exhibiting enhanced contrast capabilities and additional functionalities [15].

Iron platinum contrast agents: Superparamagnetic:

Superparamagnetic iron platinum particles (SIPPs) are believed to have significantly enhanced T2 relaxation capabilities as compared to iron oxide nanoparticles. Phospholipids have been used to encapsulate SIPPs, resulting in the formation of multifunctional SIPP stealth immunomicelles. These immunomicelles are designed to selectively target human prostate cancer cells. These contrast agents are still being researched and have not yet been tested on humans, as far as we know. The study demonstrated the synthesis and conjugation of multifunctional SIPP micelles with a monoclonal antibody targeting prostate-specific membrane antigen. Moreover, the intricate compound selectively aimed at human prostate cancer cells in a controlled environment, indicating that SIPPs could potentially exhibit tumor-specific properties in the future [16].

MRI Contrast Agents Complexes and Effect on Image:

As previously indicated, MRI contrast agents can be classified into two categories. The first group consists of paramagnetic substances, including lanthanides like gadolinium. The second category consists of transition elements, including manganese and iron.

The concept of chelation has been suggested as a means to decrease the toxicity of metal ions. The technique of chelated complex synthesis is commonly employed to produce contrast agents using metallic ions. The complexation process significantly reduces the acute and chronic harmful side-effects caused by both the metal ion and the chelating agent.

Gadolinium is utilized as a gadolinium (III) ion, as previously stated. Gadolinium (III) exhibits little affinity for serum proteins and can potentially be displaced by ligands. Lanthanide salts typically undergo hydrolysis, resulting in the formation of hydroxides. These hydroxides are absorbed by the reticuloendothelial system (RES) and accumulate in various organs of the body, such as the liver, spleen, and bone. This accumulation can potentially lead to toxicity. Lanthanide ions are eliminated by both urine and feces, whereas manganese

ions are primarily excreted through the gastrointestinal tract, specifically via the biliary route. To address the above noted issues, these components are provided in chelated forms [7].
There exist three distinct categories of gadolinium (III)-based chelates.
Ionic and hydrophilic complexes encompass gadolinium (III) diethylenetriamine pentaacetate (Gd-DTPA, sometimes referred to as gadopentate dimeglumine), Gd(III) 1,4,7,10-tetrazacyclododecane NN′N″N‴-tetra-acetate (Gd-DOTA, gadoterate), and Gd(III) polyaspartate.
Nonionic and hydrophilic complexes refer to chelates of gadolinium (III) that are both nonionic and have an affinity for water. Examples of such complexes include Gd3-diethylenetriamine pentaacetate-bis(methylamide) (also known as gadodiamide) and Gd-HP-DO3A (also known as gadoteridol), which is a macrocyclic chelate analog of Gd-DOTA with a 2-propanol radical replacing the acetic acid function.
Ionic and lipophilic complexes refer to two distinct categories of gadolinium compounds. One example of an ionic complex is the Gd benzyl-oxy-methyl derivative of diethyltriamine pentaacetate dimethylglucamine salt, commonly known as GdBOPTA or gadobenate dimeglumine. Another example is the Gd ethoxybenzyl diethylentriamine pentaacetate, also known as Gd-EOB-DTPA or gadoxetate [7,17].
With the exception of dysprosium-based compounds, paramagnetic contrast agents are positive agents that have comparable effects on both T1 imaging and T2 imaging. Nevertheless, because to the significantly larger T1 of tissues compared to T2, the primary impact at low doses is the shortening of T1. The tissues that absorb these drugs exhibit high signal intensity on T1-weighted imaging.

Negative contrast drugs decrease T2 signals by accelerating the T2 relaxation time.
Superparamagnetic and ferromagnetic agents are included within this category. However, decreasing the size of ferromagnetic particles leads to the permanent loss of their magnetic properties and a transformation into superparamagnetic particles. Depending on the size and coating of the particles, these chemicals may also function as T1 agents [18].

Contrast Media for Radiography and CT:

A positive contrast agent has a much greater ability to reduce the intensity of X-rays compared to the soft tissues of the body. When used in the correct concentration and dosage, it can be applied to, or even reach, the specific bodily system being scanned. The chemicals can be categorized into two groups: (1) water-soluble compounds having iodine and (2) non-water-soluble compounds containing barium. The elements barium and iodine exhibit significant X-ray absorption within the wavelength range of 0.02 to 0.3 nm, which is the same range employed in diagnostic radiology. A negative contrast agent exhibits lower X-ray absorption compared to soft tissue. Water and air can function as negative contrast agents [1].

Contrast media containing barium-based agents

The gastrointestinal system is commonly examined with a highly insoluble substance called barium sulphate (BaSO4). This substance is typically supplied orally or rectally in the form of a finely split aqueous suspension, with a concentration of 0.3 to 1 g dry weight per millilitre. Barium sulfate is typically not absorbed as it passes through the digestive tract. It has the potential to spill over into the lungs and seep into the mediastinum, the tissue around the rectum, or the intraperitoneal cavity, resulting in the formation of granuloma and, in some cases, deadly reactions. Hence, in cases where there is a suspicion of aspiration, the presence of a fistula connecting the esophagus and lungs, or a perforation in the gastrointestinal system, it is advisable to refrain from using barium sulphate. The infiltration of fluid into the blood vessels poses a significant risk to life, necessitating vigilance during the investigation to promptly commence appropriate therapy. Barium can lead to constipation and increase inflammation in ulcerative colitis, perhaps causing peritonitis due to perforation [19].
Iodine, with an atomic number of 53 and an atomic weight of 127, is the sole element that has been conclusively demonstrated to be suitable for widespread application as an intravascular contrast agent in radiography, including angiography and CT scans. The iodine is responsible for the radiopacity of the contrast medium. The other elements in the molecule do not contribute to radiopacity, but they serve as carriers for the iodine. This significantly enhances the solubility of the molecule and dramatically reduces its toxicity. The challenge has consistently revolved on the method of securely packaging iodine to ensure its safe delivery into highly delicate vascular systems, such as the brain, heart, and kidneys. This delivery must be accomplished with significant quantities of iodine in order to achieve sufficient radiopacity. Certain agents can be introduced into the cerebrospinal fluid without

Significant complications.

It is likely that organic substances containing iodine will continue to be the fundamental components of all intravascular contrast agents in the foreseeable future. Since the 1950s, four different chemical formulations of iodine-based contrast media have been introduced for clinical use. All four compounds are derivatives of a benzene ring with three iodine atoms located at positions 2, 4, and 6 in individual units, and six iodine atoms per molecule in dimeric form. These compounds exhibit high water solubility, low solubility in lipids, low toxicity, weak binding affinities for proteins, receptors, or membranes, and have molecular weights below 2000 [20].

High-Osmolar Ionic Contrast Media

All ionic monomers consist of salts containing sodium or meglumine (Nmethylglucamine) as the cation that does not show up on X-rays, and a radiopaque anion consisting of a completely substituted benzoic acid ring with three iodine atoms. The anions mentioned include diatrizoate, ioxitalamate, and iothalamate. Every molecule fully separates into two ions when placed in water— one cation that is not visible on X-rays and one anion that contains three iodine atoms that is visible on X-rays. This results in a particle ratio of 3:2 for iodine. Their hypertonicity is significantly high, measuring around 1600 mosmol/kg water at 300 mgI/kg, in contrast to the normal osmolality of 300 mosmol/kg water. Currently, the utilization of high-osmolar monomeric contrast media intravascularly is infrequent, as they have been largely substituted by non-ionic low-osmolar contrast media [21].

Low-Osmolar Ionic Contrast Media

Ioxaglate is the sole compound within this category. The compound consists of a combination of sodium and meglumine salts. These salts are derived from a mono acidic double benzene ring, with each benzene ring containing three iodine atoms at locations C2, C4, and C6. The overall molecule consists of six iodine atoms. When in solution, each molecule dissociates into a radiopaque hexa-iodinated anion and a non-radiopaque cation, which might be sodium and/or meglumine. Ioxaglate has an iodine-to-particle ratio of either 6:2 or 3:1. The osmolality is comparable to that of the non-ionic monomers [1].

Conclusion:

Throughout the previous 30 years, numerous contrast agents have been created for utilization in clinical settings, with a few of them being removed due to safety apprehensions. These contrast agents exhibit variances in their clinical implications, modes of action, safety, pharmacokinetics, and pharmacodynamics. Presently, researchers are investigating advanced MRI agents that are both newer and safer. These agents have the ability to specifically target organs, sites of inflammation, and specific cancers. The aim is to develop contrast agents that have a greater ability to detect and diagnose diseases.

References:

1. Themes U. Intravascular Contrast Media for Radiography, CT, MRI and Ultrasound. Radiology Key. Published March 2, 2016. https://radiologykey.com/intravascular-contrast-media-for-radiography-ct-mriand-ultrasound/
2. Lusic H, Grinstaff MW. X-ray-computed tomography contrast agents. Chem Rev. 2013;113(3):1641-1666. doi:10.1021/cr200358s
3. Rogers DC, Tadi P. Intravenous contrast. 2020
4. Seeram E. Computed Tomography: A Technical Review. Radiol Technol. 2018 Jan;89(3):279CT-302CT.
5. Mazonakis M, Damilakis J. Computed tomography: What and how does it measure? Eur J Radiol. 2016 Aug;85(8):1499-504
6. Heshmatzadeh Behzadi A, Farooq Z, Newhouse JH, Prince MR. MRI and CT contrast media extravasation: A systematic review. Medicine (Baltimore). 2018;97(9):e0055. doi:10.1097/MD.0000000000010055
7. Xiao Y, Paudel R, Liu J, Ma C, Zhang Z, Zhou S. MRI contrast agents: Classification and application (Review). International Journal of Molecular Medicine, 2016;38, 1319-1326. https://doi.org/10.3892/ijmm.2016.2744
8. Tang JB, Sheng YQ, Hu HJ and Shen YQ. Macromolecular MRI contrast agents: structures, properties and applications. Prog Polym Sci. 2013;38:462– 502.

9. Geraldes CFGC and Laurent S. Classification and basic properties of contrast agents for magnetic resonance imaging. Contrast Media Mol Imaging. 2009;4:1–23.
10. Gandhi SN, Brown MA, Wong JG, Aguirre DA and Sirlin CB. MR contrast agents for liver imaging: what, when, how. Radiographics. 2006;26:1621– 1636.
11. Shokrollahi H. Contrast agents for MRI. Mater Sci Eng C. 2013;33:4485–4497.
12. Yurt A and Kazanci N. Investigation of magnetic properties of various complexes prepared as contrast agents for MRI. J Mol Struct. 2008;892:392– 397.
13. Zhen Z, Xie J. Development of manganese-based nanoparticles as contrast probes for magnetic resonance imaging. Theranostics. 2012;2(1):45-54. doi:10.7150/thno.3448
14. Paratala BS, Jacobson BD, Kanakia S, Francis LD, Sitharaman B. Physicochemical characterization, and relaxometry studies of micro-graphite oxide, graphene nanoplatelets, and nanoribbons. PLoS One. 2012;7 (6):e38185. doi:10.1371/journal.pone.0038185
15. Na HB, Song IC and Hyeon T. Inorganic nanoparticles for MRI contrast agents. Adv Mater. 2009;21:2133–2148.
16. Taylor RM, Huber DL, Monson TC, Ali AM, Bisoffi M, Sillerud LO. Multifunctional iron platinum stealth immunomicelles: targeted detection of human prostate cancer cells using both fluorescence and magnetic resonance imaging. J Nanopart Res. 2011;13(10):4717-4729. doi:10.1007/s11051-011-0439-3
17. Bumb A, Brechbiel MW, Choyke P. Macromolecular and dendrimer-based magnetic resonance contrast agents. Acta Radiol. 2010;51(7):751-767. doi:10.3109/02841851.2010.491091
18. Verloh N, Utpatel K, Haimerl M, et al. Liver fibrosis and Gd-EOB-DTPAenhanced MRI: A histopathologic correlation. Sci Rep. 2015;5:15408. Published 2015 Oct 19. doi:10.1038/srep15408
19. Sireci S. Clinical utility of barium sulfate products: Formulation determines appropriate use. Applied Radiology, 2021;50(4), 1-7.
20. Mesbahi A, Famouri F, Ahar MJ, Ghaffari MO, Ghavami SM. A study on the imaging characteristics of Gold nanoparticles as a contrast agent in X-ray computed tomography. Polish Journal of Medical Physics and Engineering, 2017;23(1), 9.