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Assessment of adverse reactions to the use of contrast agents in diagnostic imaging exams: a narrative review

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Abstract: Contrast media are medicinal solutions enhancing diagnostic radiology's imaging quality by distinguishing anatomical structures. These widely used exams involve pharmaceutical agents, yet adverse reactions can arise. This study targets primary risks and adverse reactions tied to major contrast media in radiology. It assesses current concepts and protocols to minimize these reactions. Techniques for contrast-enhanced images demand element-based substances: iodinated, barium-based, and gadolinium-based contrasts. Adherence to manufacturer's guidelines and implementing prevention and adverse reaction procedures is vital. This study includes angiography, urography, transit studies, CT scans, and MRI as key contrast-enhanced exams. Employing a qualitative approach, it conducts a literature review. Neglecting risk assessment and safe administration can cause substantial disruptions due to adverse reactions. Protocols like desensitization and life support from a skilled medical team, alongside established protocols, reduce patient fatality risks.

Keywords: Contrast medium; Adverse reactions; Diagnosis.

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1. Introduction

One year after the discovery of X-rays by physicist Roentgen on November 8, 1895, studies were published that utilized contrast enhancement. The conducted examination was a radiograph of the stomach and intestines of a pig, with the organs filled with lead subacetate for better X-ray absorption. Therefore, the image demonstrated the presence of contrast agents. According to Augusto et al. [1], the representation of contrast agents is characterized as medicinal solutions that enhance the quality of imaging in diagnostic imaging exams, by differentiating anatomical structures. These examinations using pharmaceuticals are performed as diagnostic methods; however, their use can lead to the occurrence of adverse reactions in the patient's body [2].

These techniques have been improving over the years with the aim of facilitating the distinction of structures in their normal or pathological state. Depending on the imaging examination modality, different substances can be used, administered intravenously, orally, or rectally. Iodine-based contrast agents can be categorized as ionic and non-ionic. There are also Barium-based contrast agents and Gadolinium-based contrast agents, the latter being exclusively used in magnetic resonance imaging. Adverse reactions to contrast agents are common and include immediate hypersensitivity reactions, which are frequent and can occur within 1 hour after the contrast administration. Allergic reactions

have become less frequent with the use of non-ionic compounds. Additionally, some precautions must be taken regarding the storage of contrast agents, aiming to minimize these reactions.

The purpose of this study is to address the main risks and inherent adverse reactions related to the use of major contrast agents utilized in radiology, as well as the evaluation of current concepts and adopted protocols to minimize adverse effects in a simple and comprehensive manner.

2. Contrast Media

Radiology is a branch of medicine in which images of the human body are used to aid in the diagnosis and treatment of pathologies. The main advantage is that internal structures of the human body can be identified in a non-invasive manner. The clarity of the image is achieved through contrast agents, which provide a significant advancement for diagnosis [3]. Techniques for obtaining contrast-enhanced images involve the use of substances based on specific elements: iodine-based contrast, barium-based contrast, and gadolinium-based contrast. These chemical agents are also known for their positive or radiopaque effects on images [4].

Radiological contrast agents are compounds introduced into the body through various routes, allowing for increased definition of radiological images by enhancing contrast. This practice results in the capture of high-definition images and, consequently, greater accuracy in the reports of these diagnostic imaging examinations [3].

3. Iodinated Contrast

Iodinated contrast media can be administered orally, rectally, or intravenously. Orally, they are used to identify structures in the digestive tract. When administered intravenously, they provide better enhancement of internal organs and blood vessels [4]. Iodinated contrasts can be categorized based on their chemical nature, solubility, composition, route of administration, and dissociation capacity, as either ionic or non-ionic. Ionic iodinated contrast is one that, when in solution, dissociates into particles with negative and positive charges, whereas non-ionic contrast media do not release particles with electric charge. Non-ionic iodinated contrast, due to the absence of charged ions, is a more stable and safer contrast medium. Non-ionic contrast offers a lower likelihood of adverse reactions; thus, they are more commonly used nowadays [5].

4. Barium Sulfate

Barium sulfate is an insoluble salt in both water and fat, with the chemical formula $BaSO_4$. It is administered orally and/or rectally. This contrast should never be applied to the patient intravenously or endocavitarily, as it can lead to the patient's death in a short time. The substance is primarily used to better visualize structures of the digestive system such as the stomach, esophagus, duodenum, and can be used for evaluating intestinal transit. Barium sulfate serves the purpose of filling the digestive and gastrointestinal system, also referred to as double-contrast examinations. This occurs in exams like the barium enema, where both barium sulfate and air are introduced into the intestine. Barium sulfate is included in the World Health Organization's list of essential medicines and is considered highly effective when used correctly. Prior to being diluted in a solvent for the examination, its original form is solid (powder) and some versions are flavored to improve taste during patient ingestion [6].

5. Gadolinium Contrast

Gadolinium-based contrast media are found in nature. It is a chemically complex element that exists as a crystal with a white-silvery appearance. In medicine, gadolinium is exclusively used in the form of compounds designed to enhance imaging examinations. Gadolinium is a heavy metal that is highly toxic to the human body, and its ad-

ministration is only possible because it is bound to other substances known as chelates. Diethylene triamine pentaacetic acid (DTPA) is one of the most used chelates in contrast agents for Magnetic Resonance Imaging (MRI) exams. The types of gadolinium-based contrast agents available in the market can be divided into two categories based on the chelating agent that carries gadolinium in the molecule. Therefore, gadolinium-based agents are considered safer than iodinated contrasts used in conventional radiology and computed tomography (CT) scans [7].

6. Pre-Contrast Procedures

For each contrast used, it is necessary to follow the guidelines and protocols established for the prevention and treatment of adverse reactions. In this process, it's essential to assess potential risks and benefits, discuss imaging methods to be used and their accuracy, obtain signed informed consent, and establish strategies for handling complications if they occur [8]. Before applying the contrast, it's important to consult with the patient and address any questions, avoiding anxiety, evaluate their medical history and clinical condition, and assess the consequences of using the contrast, including checking for risk factors such as medications in use. Despite all efforts, it's nearly impossible to predict the occurrence of adverse reactions, so every patient should be categorized by risk profile. Patients should fill out a questionnaire called Anamnesis, with the help of a responsible professional who alerts the team about the potential risk of adverse reactions. Patients with a history of allergies are more prone to developing adverse reactions to contrast.

The clinical interview called Anamnesis consists of a form with questions, ranging from basic patient information like age and gender to clinical data about diseases, allergies, and previous exams [9]. According to Carmo [3], collecting this information aids in identifying patient risk conditions. Ethical considerations related to contrast exams need to be approached with caution and responsibility, beginning with presenting, and explaining to the patient all the procedures that will be performed, including possible complications and adverse reactions. Prior to the exam, the patient should sign a responsibility agreement, a document that should be reviewed before any procedure begins [10].

7. Primary Contrast-Enhanced Examinations

7.1 Angiography

Angiography is a radiological technique developed to detect anomalies in blood vessels, such as arterial dilations, inflammation, abnormal configurations, or vascular obstructions. Contrast is injected into the vessel under examination through a thin catheter inserted into the femoral, brachial, or carotid artery. The site is anesthetized, and a needle is inserted. A long, thin wire is introduced through the needle and the needle is then removed. A catheter is threaded over the wire into the blood vessel. The tip of the catheter is guided to the vessel to be examined, and the contrast is injected [11]. Typically, iodinated contrast is used for this examination, aimed at visualizing blood vessels. This technique is very effective in detecting diseases like arteriosclerosis and aneurysms, or it can even be used for confirmatory testing where a patient's brain death was confirmed through complementary exams like angiography. In the image, we can observe areas with absent cerebral blood flow [11].

7.2 Excretory Urography

Excretory urography is an examination aimed at evaluating the urinary system: kidneys, ureters, bladder, and urethra, identifying the entire collecting portion of the urinary system and assessing the functional capacity of the kidneys. The images demon-

strate contrast in the patient's excretory system. This is a radiological examination in which iodinated contrast is used. The contrast medium is administered via intravenous injection, and from that point on, a sequence of images is taken. The examination is indicated for investigating various diagnostic hypotheses, including renal and ureteral calculi, abdominal or pelvic masses, flank pain, cysts, renal insufficiency, hypertension, urinary tract infections, renal trauma, tumors, among other indications [12].

7.3 Intestinal Transit Examination

The intestinal transit examination assesses the entire small intestine up to the beginning of the large intestine. It can be performed to evaluate both the structure and functionality of the intestinal tract. This examination is recommended in cases of inflammatory bowel disease, diarrhea, constipation, tumors, and others. The contrast medium used is barium sulfate. This contrast medium enables the visualization of the small intestine on the X-ray equipment screen. Several X-rays in different positions are taken after the ingestion of barium to achieve satisfactory anatomical visualization. The images are repeated every 30 minutes until the contrast reaches the beginning of the large intestine. This examination should never be performed in cases of abdominal perforation, as barium is an insoluble compound and cannot be eliminated through the bloodstream. Barium is excreted through the feces, and after the exam, it's important for the patient to stay well-hydrated and have a fiber-rich diet to facilitate proper elimination of the barium [13].

7.4 Computed Tomography

Computed Tomography (CT) plays a crucial role in the hospital's care activities by confirming or complementing diagnostic findings. The fundamental principle of CT is the use of very thin X-ray beams combined with advanced computer technology to obtain detailed images, thereby enhancing the visualization of body segments. This examination has contributed to the evolution of medicine and has also required the development and refinement of specialized knowledge among interdisciplinary radiology teams to provide specialized and excellent care to the population. CT is a painless procedure in which the patient needs to lie still on a hydraulic and adjustable bed while the CT scanner records images of the area being examined. The risks of the exam are related to radiation exposure and the administration of iodinated contrast, with the latter often being required for better visualization of the studied anatomical structures [14].

Iodinated contrast exhibits radiopaque properties as well as potential adverse effects, highlighting the importance of preventive actions discussed with emphasis in this work. Iodinated contrast is usually administered orally, rectally, and/or intravenously prior to or during the procedure. This substance enhances the definition of CT images, improving the quality of morphological information provided by the method. Iodinated contrast can be classified, based on its dissociation capacity, as ionic or non-ionic. Ionic iodinated contrast dissociates into particles with positive and negative charges in solution, while non-ionic contrast does not release electrically charged particles.

The number of particles relative to the volume of solution determines the contrast's osmolarity. Therefore, ionic iodinated contrast has higher osmolarity than non-ionic contrast. Other properties of the contrast relate to its density and viscosity. The higher the density and viscosity, the more resistance the contrast will have to flow, resulting in a slower injection speed and making its dilution in the bloodstream more difficult. It's important to note that all these properties are linked to the efficacy and safety of iodinated contrast agents. The ideal contrast agent should enhance image quality without causing any adverse reactions (AR), but such a substance is not yet available. Adverse reactions to contrast media (CM) can occur after single or multiple administrations. These reactions are commonly classified by their severity: mild, moderate, and severe [15-16].

7.5 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging is one of the examinations that currently provide high-quality images of the interior of the body, including the brain, spine, abdomen, ligaments, joints, and more recently, the heart and blood vessels. For over 30 years, this examination has been continuously refined and has proven highly valuable in various medical fields. MRI produces three-dimensional images non-invasively without the risks of ionizing radiation, but it involves a very strong magnetic field. The contrast medium used in this type of examination is gadolinium, which is administered to the patient intravenously. Since pure gadolinium is highly toxic to the human body, its administration is only possible when it's bound to other substances called chelates. The recommended dosage for most MRI examinations is approximately 0.1 mmol/kg of body weight. The dosage may be doubled for angiographic exams. Gadolinium contrast is contraindicated for individuals with ferromagnetic implants or electronic devices incompatible with the magnetic field [14].

In this examination, contrast assists in detecting small tumors that are often difficult to identify. It also helps distinguish whether the detected tumor is benign or malignant [8]. MRI facilitates the diagnosis of various pathologies and all types of tumors, including cerebral malformations, ischemic and hemorrhagic vascular accidents, vascular malformations, cerebral aneurysms, venous thromboses, hydrocephalus, herniated discs, myelin lesions, cerebral hematomas, infections, and even investigates the causes of seizures and epileptic seizures. This examination is more sensitive than computed tomography, offering better lesion visualization and allowing a more detailed analysis of diverse pathologies, thus guiding potential therapeutic approaches more accurately [8].

According to Muñoz et al. [17], there is a possibility of developing nephrogenic systemic fibrosis (NSF) due to the use of gadolinium. NSF is a recently identified, uncommon pathology that can manifest as a severe adverse reaction. The disease primarily affects individuals with chronic renal insufficiency, and the best prevention method is to monitor each individual's glomerular filtration rate. In cases where patients exhibit low glomerular filtration rates, alternative diagnostic options should be considered, and the contrast cannot be administered [7].

8. Discussion

It is evident that contrast agents are part of a pharmacological evolution within radiology that enables accurate and high-quality diagnoses. However, adverse reactions to contrast agents can be problematic if the risks are not evaluated and administration is not carried out safely, planned, with the use of proper protocols prior to the exams [14]. In this context, adverse reactions can be defined as any harmful or unwanted effect resulting from the administration of contrast agents at appropriate doses. Patients with a higher potential for developing allergies or adverse reactions to contrast agents are referred to as hypersensitive. In such cases, radiologists prescribe pre-treatment with antihistamines and corticosteroids, anti-allergic medications capable of mitigating potential allergic reactions to the drug. In every contrast-enhanced examination, it is essential for the patient to complete a pre-prepared anamnesis questionnaire, found in all radiodiagnostics departments. This questionnaire includes inquiries to analyze possible allergic histories. The main contraindications for the use of contrast agents depend on the nature of each drug, and renal insufficiency is an absolute contraindication for any contrast agent [16].

Adverse reactions can be classified according to their severity level, and depending on the main signs and symptoms, they are classified as mild, moderate, severe, and fatal. Mild reactions are the most common, have a short duration, and symptoms can spontaneously subside without the need for medication. Moderate or intermediate adverse reactions are more noticeable than mild ones, requiring greater care with the need for medical intervention, observation, and treatment. In these cases, it is important to always

instill confidence and reassurance in the patient, so they do not panic, and to immediately alert the medical team. Severe reactions can result from the progression of clinical conditions originating from mild or moderate reactions. They are rarer and require urgent hospitalization due to the threat to the patient's life, as the clinical condition can lead to death. Fatal reactions are the most common causes of death associated with the use of contrast agents [18].

The half-life of intravenously administered iodinated contrast agents is approximately two hours, and the dose is eliminated from the body within about forty-eight hours [18]. The risk of acute reactions to Gadolinium (Gd) contrast use is significantly lower than that of iodinated contrast agents, but it can still pose risks to patients with chronic renal diseases or those with allergies or greater sensitivity. Hence, the importance of patient history taking and care by the professionals involved in the technique application is emphasized, always investigating allergy or pre-existing disease history and observing any signs or symptoms during and after the contrast agent application [19].

The most common mild reactions include nausea, vomiting, urticaria, and headache. Predominant local reactions include irritation, burning, and a sensation of coldness. Adverse reactions after intravenous injection of Gd are more frequent in patients who have previously experienced reactions to any type of internal contrast. Studies show that 16 out of 75 patients who develop allergic reactions to Gd experienced new reactions in subsequent injections. Patients with a history of previous reactions to iodinated contrast agents are more than twice as likely to have an allergic reaction to Gd. Individuals with asthma are also more prone to adverse reactions to Gd. Patients with a history of allergies, in general, have an increased risk of developing adverse reactions compared to patients without a history of allergies [19].

Cases of hypersensitivity to barium sulfate-based contrast agents are very rare. The main disadvantage is related to the presence of gastrointestinal tract perforations, as barium can penetrate the mediastinal or peritoneal cavity. Once in the body, barium is not absorbed or eliminated, remaining in the tissues, and potentially causing granulomatous reactions. The presence of barium can lead to peritonitis, characterized by severe abdominal adhesion associated with pain, as barium can cause significant complications by obstructing the intestinal lumen, leading to constipation or complete obstruction. Sedentary, dehydrated, elderly, and newborn patients are at higher risk of impaction. Adequate fluid intake, immediate elimination of barium through feces, and the use of laxatives post-procedure minimize risks [20].

According to the Brazilian College of Radiology [21], if it were possible to choose an ideal contrast agent, the best choice would be a solution that does not trigger allergic reactions. However, such an agent does not yet exist. Measures for reducing these reactions can be considered by implementing preventive measures from the beginning of the entire process. Cremonini [22] states that the use of non-ionic iodinated contrast agents has a lower probability of adverse reactions compared to ionic contrast agents. However, despite the greater safety offered by non-ionic contrast due to its low osmolarity, there are cost-related barriers associated with these agents, impacting healthcare services. Katayama et al. [23] reports the effectiveness of non-ionic iodinated contrast agents, resulting in lower rates of adverse reactions.

Silva [24] emphasizes that heating the contrast agent to body temperature reduces its viscosity, making it more tolerable during intravenous administration. Juchem [15] also describes pre-heating the contrast agent using ovens, which not only reduces viscosity but also improves the injection process, providing greater comfort to the patient during administration. Hence, the need for protocols and interventions to prevent mild, moderate, or severe adverse reactions is evident. Assessing risks and implementing preventive measures provides a comprehensive understanding and effective strategies to reduce incidents. It is also important to consider that every patient undergoing a contrast-enhanced examination is susceptible to allergic risks, making the adopted measures both safe and efficient. Future research on contrast agents and adverse reactions should

address technological innovations and studies involving pathologies related to contrast-enhanced techniques, presenting safer alternatives with fewer contraindications to their use, avoiding complications such as nephrogenic systemic fibrosis and tissue accumulation, as observed in some cases due to the use of gadolinium.

9. Conclusion

Based on the literature, it can be concluded that contrast agents pose risks related to adverse reactions, with iodinated contrasts representing the highest risk, followed by gadolinium-based contrasts and barium contrasts. Therefore, established protocols preceding the use of contrast agents prevent many accidents. The involvement of a prepared medical team reduces the risk of death for patients who develop allergies, regardless of the examination technique used in radiology departments.

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References

1. Augusto RAPX, Xavier MCH, Eduardo AHA. Efetividade de intervenções de enfermagem preventivas de respostas adversas a meio de contraste iodado: protocolo de revisão sistemática. Enfermería Actual de Costa Rica. 2020;39:245-254.
2. Pozzobon A, Trindade FR. Avaliação das reações adversas ao uso de contrastes em exames de diagnóstico por imagem. Rio Grande do Sul: Editora Cinergis, 2017.
3. Carmo ALF, Silva FMD, Buzzo PRJ, Rocha G. Contraste iodado, risco e reações. Mato Grosso do Sul: Editora Revista conexão eletrônica; vol 14, 2017.
4. Juchem BC, Dall Agnol, Magalhães AMM. Contraste iodado em tomografia computadorizada, prevenção de reações adversas. Brasília: editora revista brasileira de enfermagem, 2004.
5. Martín CM, Lorigados CAB, Grunkraut AS, Zardo MK, Pinto ACBCF. Meios de contraste iodado, propriedades físico-químicas e reações adversas. Curitiba: Editora Rev. Acad Ciênc. Agrár Ambiental, 2014.
6. Schüler CN. Estudo radiográfico com ingestão de bário na rotina clínica: um estudo prospectivo em pacientes com tosse crônica. Porto Alegre: Universidade federal de ciências da saúde de Porto Alegre – UFCSPA, 2016.
7. Karam MAH. Risco de Fibrose Sistêmica Nefrogênica com o Uso de Contraste à Base de Gadolínio em Doença Renal Crônica. J Bras Nefrol. 2008;30(1):66-71.
8. Hage MCNS, Iwasaki M. Imagem por ressonância magnética: princípios básicos. São Paulo: Editora Ciência Rural, Santa Maria, online, 2018.
9. Fontanella T. Terapia Floral: Florais de Saint Germain. [s.l.]: Espaço Ânima; 2010. 294 p.
10. Fenelon S. Aspectos ético-legais em Imaginologia. Radiologia Brasileira. 2003;36(1):3-6.
11. Laureano VS, Zirretta JC, Koch HA. Angiografia por tomografia computadorizada dos aneurismas intracranianos. Rio de Janeiro: Editora Radiol Bras, 2002.
12. Dyer RB, Chen MYM, Zagoria RF. Urografia intravenosa: técnica e interpretação. São Paulo: Editora Radiol Bras vol 35, 2002.
13. Naci MS, Rocha VMB, Mello RAF, Jauregui GF, Couto LS, Gonçalves JRO, Santos AASMD. Análise retrospectiva do trânsito do delgado em um serviço de radiologia de hospital geral. Rio de Janeiro: Editora Radiol Bras, 2004.
14. Guimaraes MD, Schuch A, Hochhegger B, Gross JL, Chojniak R, Marchiori E. Ressonância magnética funcional na oncologia estado da arte. Rio de Janeiro: Radiol Bras Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, 2014.
15. Juchem BC. Contraste iodado em tomografia computadorizada: reações adversas imediatas em pacientes hospitalizados. 2005.
16. Juchem BC, Dall Agnol MC. Reações adversas imediatas ao contraste iodado intravenoso em tomografia computadorizada. Rio de Janeiro: Editora Revista Latino-am Enfermagem, 2007.
17. Muñoz SC et al. Contrastes baseados em gadolínio utilizados em ressonância magnética. Radiologia. 2014;56:21-28.
18. Silva EA. Meios de contraste iodado. In: Colégio Brasileiro de Radiologia. Assistência à vida em radiologia: guia teórico e prático. São Paulo; 2000.
19. Jorge EJ, Santos AC, Koenigkam SM, Nogueira BMH, Muglia VF. Complicações do uso intravenoso de agentes de contraste à base de gadolínio para ressonância magnética. São Paulo: Editora Radiol Bras, 2008.
20. Almiro MM, Maia C, Branco L, Pedrosa C, Romariz J, Praça F, Costa H. Reações de hipersensibilidade a meios de contraste em idade pediátrica. Revista nascer e crescer de pediatria do centro hospitalar VOL XIX, 2016.
21. Silva EA, Oliveira LAN. Meios de contrastes iodados. São Paulo: Editora Colégio Brasileiro de Radiologia, 2000.

22. Cremonini CCC. Avaliação das reações adversas agudas após administração endovenosa de contraste iodado iônico e não-iônico em hospital oncológico. [dissertação de mestrado]. Botucatu: Universidade Estadual Paulista; 2010.
23. Katayama H, K Yamaguchi, Kozuka, T, Takashima T, Seez P, Matsuura K. Reações adversas aos meios de contraste iônicos e não-iônicos: um relatório do Comitê Japonês sobre a Segurança dos Meios de Contraste. Editora Radiol Bras, 1990.
24. Silva HCS. Avaliação do extravasamento do meio de contraste iodado em pacientes oncológicos submetidos à Tomografia Computadorizada. 2016.