REVIEW

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Evaluation of the safety profile of CT and MRI contrast agents based on iodine and gadolinium

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Summary

Objectives: The purpose of the study was to investigate the safety of contrast agents in the field of medical radiology.

Methods: We conducted a comprehensive literature review through databases such as PubMed, Google Scholar, Scopus, and ScienceDirect, with the selection of relevant articles based on keywords, publication in English, study design, and publication criteria from 2020 to 2024.

Results: In the course of the study, we determined that iodine-containing contrast agents are often used in medical imaging, but their safety is a concern, especially in patients with renal impairment and a tendency to allergic reactions. It is recommended to observe a 4-12 hours interval between procedures to minimise the risk of contrast-induced nephropathy. Iodised contrasts are more likely to cause adverse reactions compared to gadolinium-based contrasts, but serious cases such as anaphylaxis remain rare (0.06%). Low-concentration iodine-containing contrasts for cerebral angiography have shown high safety, reducing toxic effects. Barium contrast agents have demonstrated a high level of safety when used in diagnostics, including procedures such as oral barium test. Special attention was paid to reducing radiation exposure and compliance with safety protocols during the COVID-19 pandemic, which prevented the spread of infections. Contrast agents based on linear gadolinium more often contribute to its deposition, which could be associated with potential long-term risks, although their clinical consequences have not been fully examined. In contrast, macrocyclic gadolinium chelates show better stability and less often cause such effects, which makes them preferable in clinical practice.

Conclusions: The introduction of strict recommendations on the use of gadolinium-containing contrast agents has reduced the incidence of nephrogenic systemic fibrosis, but further studies on their accumulation in the body remain relevant.

KEYWORDS: *iodised contrast media, computed tomography, magnetic resonance imaging, gadolinium, barium*

INTRODUCTION

Contrast agents play a key role in radiology, substantially improving the quality of imaging and diagnosis of various diseases. Their use allows more accurate identification of pathological conditiones such as tumors, inflammation, vascular abnormalities, and organ disorders.

Due to the increasing number of diagnostic procedures such as magnetic resonance imaging (MRI), computed tomography (CT), and radiography, contrast agents are becoming an indispensable tool in clinical practice. However, safety issues and potential side effects associated with the use of contrasts, such as gadolinium and iodine-containing drugs, make the subject of their use especially relevant in the context of modern medicine.

For contrast enhancement in CT, iodinated agents are most commonly used. These substances possess high radiopacity and enable detailed visualisation of vascular structures, parenchymal

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organs, and body cavities. Despite their diagnostic efficacy, iodinated contrast agents are associated with potential risks, including nephrotoxicity, allergic reactions, and iodine-induced thyrotoxicosis. These risks are particularly elevated in patients with chronic kidney disease, hyperthyroidism, or a history of allergic conditions. The safety of repeated administration, as well as the influence of iodine concentration, osmolality, and viscosity, remains the subject of ongoing clinical research.

In MRI, the primary contrast agents are gadolinium-based compounds. These agents alter tissue relaxation properties and improve the visualisation of pathological lesions, particularly within the central nervous system. However, several studies have demonstrated the ability of gadolinium to accumulate in deep brain structures, even in patients with normal renal function, raising concerns about potential long-term effects. Particular caution is warranted with linear gadolinium-based agents, which exhibit lower chemical stability, whereas macrocyclic compounds are considered more stable and carry a reduced risk of deposition. The risk of nephrogenic systemic fibrosis in patients with end-stage chronic kidney disease represents another significant factor necessitating caution in the clinical use of gadolinium-based contrast agents.

The impact of contrast enhancement parameters on radiomics and artificial intelligence (AI)-based diagnostics is an emerging area of research in medical imaging. Radiomics involves the extraction of quantitative features from medical images, which can then be analyzed to provide insights into disease characteristics, such as tumor texture, shape, and heterogeneity. The use of contrast agents plays a pivotal role in enhancing the quality of images, allowing for better delineation of tissues and abnormalities, which is essential for accurate radiomic feature extraction.

Contrast enhancement can significantly influence the accuracy and reproducibility of radiomic features, as the selection of contrast agent type, dose, and imaging timing can alter the visibility and enhancement of certain tissues or lesions. For example, iodine-based contrast agents used in computed tomography (CT) can improve the visualization of vascular structures and tumors, whereas gadolinium-based agents used in magnetic resonance imaging (MRI) can enhance tissue contrast, particularly in soft tissues and brain lesions. The timing of contrast administration, such as pre-contrast, arterial, and venous phases, also affects the enhancement pattern and subsequent feature extraction.

AI-based diagnostic systems, particularly those leveraging machine learning (ML) and deep learning (DL) algorithms, heavily depend on the quality and consistency of the input data. Inaccurate or inconsistent contrast enhancement parameters can introduce variability into the radiomic features, potentially affecting the performance of AI models. Therefore, optimizing contrast parameters, such as the appropriate contrast agent, dose, and injection timing, is critical to ensure that AI models receive reliable and reproducible data for training and validation. AI techniques, such as convolutional neural networks (CNNs), can help analyze the effects of different contrast protocols on diagnostic outcomes by learning patterns and predicting clinical parameters like tumor classification, staging, and treatment response.

In the context of AI-assisted diagnosis, understanding the impact of contrast parameters allows for the refinement of imaging protocols that maximize diagnostic accuracy. By integrating AI with radiomics, clinicians can achieve more personalized and precise assessments, enhancing the clinical decision-making process. Furthermore, AI can assist in standardizing imaging protocols to reduce operator-dependent variations in contrast-enhanced imaging, which is essential for multicentre studies or longitudinal patient monitoring. Ultimately, the optimization of contrast enhancement parameters, in combination with AI and radiomics, promises to improve diagnostic precision, treatment planning, and patient outcomes across a wide range of clinical applications.

Gadolinium-containing drugs can accumulate in tissues, especially in the brain, raising concerns about their long-term safety. Some contrast agents can cause toxic reactions, especially in patients with impaired renal function or other chronic diseases. In addition, there is a risk of allergic reactions, including severe anaphylactic reactions, when using iodine-containing and some other contrast agents. Pregnant women, children, and patients with chronic diseases require a special approach in choosing contrast agents. Therefore, the investigation of the use of these substances in

the field of radiology has been conducted by many authors, including Didier et al.(1), Dekkers et al. (2), and MacDonald et al.(3) explored gadolinium and iron-based contrast agents that enhance cancer imaging by affecting T1 and T2 relaxation times. These agents, created from core/shell nanoparticles, improve tumor-to-normal tissue contrast, with in vivo experiments showing a significant increase in tumour contrast.

Modern technologies, including three-dimensional and four-dimensional contrast ultrasound imaging (CEUS), have demonstrated potential for enhancing diagnostic accuracy, particularly in urosonography, as noted by Rudnicki et al.(4). Intraoperative CEUS imaging is improving tumor diagnosis and treatment in adults, with potential applications in pediatric neurosurgery. Additionally, molecular imaging and localized drug delivery using ultrasound contrast agents are being actively investigated for the treatment of aggressive brain tumors.

Contrast-enhanced spectral mammography (CESM) has demonstrated potential in differentiating between malignant and benign breast lesions based on enhancement characteristics, with infiltrating cancers typically showing more pronounced signal amplification(4). The use of iodinated contrast agents has been associated with rare adverse effects, such as transient sialadenitis, particularly in elderly patients(5). These observations underline the need for careful risk assessment and monitoring of contrast-related side effects in clinical practice. Seven cases of contrast-induced encephalopathy after intravascular administration of iodine-containing contrast agents were described by Stebner et al.(6). The study included patients with an average age of 75 years. Encephalopathy developed mainly after endovascular thrombectomies and aneurysm treatment. The main symptoms included stroke-like neurological deficits, and prednisone treatment led to improvement in most cases. One patient died, but a direct link to the side effect has not been established. Wang et al.(7) examined 26 cases of Kounis syndrome (KS) in patients aged 30 to 83 years following contrast agent use, including gadolinium and iodine-containing substances. Symptoms such as chest pain and allergic reactions developed within 30 minutes of administration. Most patients recovered, though two fatalities were reported.

The use of contrast agents intravenously during pregnancy is possible, as they are well tolerated and rarely cause side effects. However, Perelli et al.(8) argued that it is preferable to conduct such examination only with strict indications when diagnosis is difficult without them, and contrast enhancement may be vital. It is important to carefully inform patients about the possible risks and benefits.

The purpose of the study is to analyse the effect of various contrast agents on the human body in the context of safety. Objectives: evaluate the safety of iodine-containing contrast agents, barium, and gadolinium-containing contrast.

MATERIALS AND METHODS

The issues of the use of iodine-containing contrast agents in patients with various pathological conditions were considered. The effect of doses of iodine-containing contrast agents on the human body, the occurrence of an allergic reaction to a contrast agent, and the effect of iodine contrast on the kidneys, liver, and brain were evaluated. Barium contrast agents for oral administration are also reviewed. The safety of barium during the COVID-19 pandemic was examined, the assessment of cancer development after the use of barium contrast, and the effectiveness of barium injections was evaluated. The use of gadolinium in patients with chronic kidney disease and multiple sclerosis was reviewed. The accumulation of various gadolinium preparations in the central nervous system, subcutaneous fat in children and adults, as well as the process of removing the contrast agent from the body, is considered. The dosage and occurrence of side effects of gadolinium and its derivatives and immediate reactions were evaluated.

The literature search was performed using databases such as PubMed, Google Scholar, Scopus, and Science Direct. The evidence-based papers that were posted on the listed databases were examined. The list of references was compiled from publications published in databases from 2020 to 2024. Literary reviews, theoretical and empirical studies, and articles with clinical and practical information were considered for inclusion in the list of references.

The following keywords were used to search for information: safety of contrast agents, use of

contrast agents, application of contrast agents, computed tomography, magnetic resonance imaging, radiography, ultrasound, safety of barium in radiology, safety of iodine-containing contrast agents in radiology, gadolinium in radiology, barium contrast agents rats, gadolinium containing contrast agents rats, iodine-containing contrast agents rats, the use of contrast agents in pediatrics, the safety of contrast agents in pregnant women, the safety of contrast agents in children, barium, gadolinium, iodine, contrast, the use of contrast agents in neurology, the effect of contrast agents on the central nervous system, the use of contrast agents in oncology, side effects when using contrast agents, the use of contrast agents in angiography, immediate allergic reactions to an iodine-containing contrast agent, allergy to barium, allergic reaction to gadolinium.

The criteria for the selection of papers included the publication of articles in English, the study being free for review, and keyword searches in databases. The selection of studies was also conducted considering the country in which the study was conducted, the date of publication in the database, the name of the first author, the name of the journal, and the design of the study. The data were extracted through careful reading and review of scientific papers. The titles of the articles, annotations, introduction, results and discussions, conclusions, and references were considered. Articles that were not accurate in their internal content, did not have a formulated annotation, were not displayed correctly in search databases, or did not have information for this study were excluded from the list of references.

RESULTS AND DISCUSSION

Iodine-containing contrast agents' efficacy and safety

Examination of the pharmacokinetics of contrast agents determined safe intervals between successive contrast-enhanced examinations depending on kidney function(9). It was recommended to adhere to a minimum interval of 4 hours between CT and angiography in patients with normal renal function, with an optimal wait of 12 hours for the complete elimination of iodine-containing contrast agents. An increase in the waiting interval is necessary in case of deterioration of renal function to reduce the risk of contrast-induced nephropathy. Iodised contrast agents (Table 1) can affect the quality of MRI, and gadolinium-containing drugs (Table 2) can change CT results, which requires consideration when planning sequential procedures. This approach helps to minimize the strain on the kidneys and avoid adverse interactions between contrast agents during frequent diagnostic examinations.

A comparative assessment of adverse reactions to the use of iodised contrast media and gadolinium-based media was conducted by Jiang et al.(10). It was determined that the frequency of adverse reactions to iodised contrast media (ICM) was substantially higher than to gadolinium-based contrast media (GBCM). Among 27,328 pa-

Table 1.

Data on iodine-containing contrast agents, their physico-chemical characteristics, and application.

Name	Structure	Ionicity	Application	Concentration (mgI/mL)	Molecular Weight (Dalton)	Osmolality (mOsm/kg at 37°C)	Viscosity (mPa·s at 37°C)	1-Butanol/Water Partition Coefficient (log P, pH 7.6 at 37°C)
Iohexol	Monomeric	Nonionic	IV	300	821	640	6.1	0.082 (-1.086)
Iopromide	Monomeric	Nonionic	IV	300	791	607	4.6	0.149 (-0.827)
Iopamidol	Monomeric	Nonionic	IV	300	777	616	4.7	0.089 (-1.050)
Iomeprol	Monomeric	Nonionic	IV	300	777	521	4.5	0.105 (-0.979)
Ioversol	Monomeric	Nonionic	IV	300	807	645	5.5	0.031 (-1.509)
Iobitridol	Monomeric	Nonionic	IV	300	835	695	6.0	-
Iodixanol	Dimeric	Nonionic	IV	320	1550	290	11.4	0.043 (-1.370)
Diatrizoate	Monomeric	Ionic	Oral	370	614	2150	8.9	0.044 (-1.356)
Ioxitalamate	Monomeric	Ionic	Oral	300	644	1710	5.3	-

Source: compiled by the author based on(9).

Table 2.

Physical and chemical characteristics of various gadolinium-containing contrast media, their osmolality, viscosity, and ability to influence T1 and T2 relaxation in the blood.

Name	Ligand	Structure	Ionicity	Molecular Weight (Dalton)	Osmolality (mOsm/kg)	Viscosity (mPa·s at 37°C)	T1 Relaxivity in Blood, 1.5T (l/mmol·s)	T2 Relaxivity in Blood, 1.5T (l/mmol·s)
Gadopentetate	DTPA	Linear	Ionic	939.0	1960	2.9	4.3	4.4
Gadodiamide	DTPA-BMA	Linear	Nonionic	537.6	789	1.4	4.6	6.9
Gadobenate	BOPTA	Linear	Ionic	1058.2	1970	5.4	6.7	8.9
Gadoxetate	EOB-DTPA	Linear	Ionic	682.0	688	1.2	7.3	9.1
Gadoteridol	HP-DO3A	Macrocyclic	Nonionic	558.7	630	1.3	4.4	5.5
Gadobutrol	BT-DO3A	Macrocyclic	Nonionic	604.7	1603	4.9	5.3	5.4
Gadoterate	DOTA	Macrocyclic	Ionic	558.6	1350	2.0	4.2	6.7
Gadopiclenol	NA	Macrocyclic	Nonionic	970.1	843	7.6	12.8	15.1

Source: compiled by the author based on(9).

tients who underwent CT with ICM, adverse reactions were observed in 0.76% of cases (207 cases), whereas among 16,381 patients who underwent MRI with GBCM, adverse reactions were recorded only in 0.15% of cases (25 cases). Statistical analysis showed that GBCM caused substantially fewer reactions compared to ICM. There were no substantial differences in the frequency of adverse reactions between different types of iodised contrast agents, such as ioversol and iodixanol, as well as between products from different manufacturers. This indicated that the safety of these drugs was similar, and preference for more expensive or imported contrasts was not required. These data emphasised the importance of the careful choice of contrast media for certain categories of patients, especially for young people and women, when the use of contrast is necessary.

Kwon et al.(11) assessed the risk of post-contrast acute kidney injury after repeated administration of iodinated contrast agents and gadolinium-containing contrast agents. 300 patients (average age 68.5 years) who underwent at least one perfusion computed tomography of the brain using ICM were included. The patients were divided into three groups: those who received a single contrast injection, and groups with repeated injections within 4 hours and in the interval of 4-48 hours. The main focus was on assessing the risk of acute kidney injury (AKI) after re-administration of contrast in a short period. When analysing only ICM in the single-dose group, AKI was recorded in 7.2% of patients, in the group with administration within 4 hours – in 13.8%, and in the group with an interval of 4-48 hours – in 8.6%. However, after a multivariate analysis considering concomitant diseases and the use of nephrotoxic drugs, no substantial association was identified between repeated doses of the contrast agent and an increase in the risk of AKI ($p>0.05$). This showed that repeated administration of ICM in short periods of time did not increase the risk of developing AKI in patients with renal function measured at levels greater than 30 ml/min/1.73 m^2. The study demonstrated the importance of monitoring kidney function and individual risk factors before prescribing repeated doses of contrast agents, but in the case of adequate renal function, the risk of kidney damage remains low.

Another study analysed the frequency and risk factors of anaphylaxis caused by iodised contrast agents in patients undergoing computed tomography with contrast(12). Of 76,194 ICM injections, anaphylaxis occurred in 45 patients, which accounted for 0.06% of all injections and 0.16% of patients. In most cases (69%), no predisposing factors were determined, and 31 patients had previously used ICM without any adverse reactions. Four patients received pre-treatment with steroids, but this did not affect the frequency of anaphylaxis. The only substantial factor associated with anaphylaxis was the type of contrast agent. Iomeprol had an increased risk (6.8) compared to iopamidol. The effect of age, gender, or premedication on the risk of anaphylaxis has not been identified. This confirmed the low incidence of anaphylaxis when using ICM, while the type of contrast agent proved to be an important predictor.

The need to modernise contrast agents for computed tomography was considered in the study by Owens et al.(13). Current clinical agents have remained unchanged for decades and have substantial drawbacks such as nephrotoxicity and a short half-life. The new generation of contrast agents should have long-term blood circulation, non-toxicity, and non-immunogenicity. Nanoparticles used as contrast agents have shown promising results and are considered key for the future of CT. The analysis of hypersensitivity to iodised contrast agents established differences in risks for several types of contrasts(14). The study covered reports of side effects, including 5,432 cases of ICM-induced hypersensitivity. Among the various agents, iomeprol demonstrated the highest risk, with an odds ratio of 24.75. Iopromide and ioversol were more likely to cause angioedema, especially in patients aged 45-64 years. Iomeprol was also the leader in the frequency of severe skin reactions, and iodixanol demonstrated the maximum frequency of side effects when considering general use. Iopamidol caused the greatest disproportion in cases of anaphylactic shock, especially in men and the elderly. The findings highlight the need for further research to improve the safety of ICM application, considering age, gender, and geographical factors.

The effect of various iodised contrast agents on the quality of coronary CT angiography using an injection protocol adapted by body surface area (BSA) was evaluated by Zhang et al.(15). The participants were divided into three groups receiving contrast agents with different iodine concentrations: ioversol 320, ioversol 350, and iopromid 370. Contrast was administered with a fixed duration of injection adapted to BSA, followed by rinsing with saline solution. The results showed that all three contrast media had the same high diagnostic quality and safety. There were no differences in contrast enhancement, image quality, radiation doses, and frequency of side effects between the groups. This confirms that different iodine concentrations in contrast agents have a similar effect on the diagnostic quality of coronary CT angiography. In the paper by Caron et al.(16), the prevalence of an allergic reaction to iodised contrast media was examined. Of the 74 patients with immediate allergic reactions to iodised contrast agents, allergy was confirmed by skin tests in 8.1% of cases. Therewith, 12.5% of patients who were repeatedly exposed to ICM had a recurrence of allergic reactions, despite the negative results of skin tests. These data indicate the limitations of existing methods for diagnosing hypersensitivity, such as skin tests. The development and implementation of additional diagnostic tools, in the form of a drug provocation test and advanced intradermal tests, can improve patient safety and improve the detection of repetitive reactions to ICM. In addition, coordinated practice among allergists is required to unify approaches to the diagnosis and treatment of such reactions.

Pregnancy-related cancer (PAC) is rare, but its cases are increasing due to the increasing age of mothers at conception(17). PAC is a cancer that is detected during pregnancy or during the first year after childbirth. Diagnosis may be delayed, as the symptoms may be disguised as physiological changes characteristic of pregnancy. Clinical management requires an interdisciplinary approach that considers both maternal and fetal safety. Ultrasound and MRI are given priority in imaging since they do not use ionising radiation. The use of iodised contrast materials is safe, but gadolinium-based contrast agents should be avoided. Radiation doses for other imaging methods (mammography, X-ray, CT) are usually below the thresholds that cause adverse effects. Important factors in the choice of treatment methods are the gestational age, the stage of cancer, and the patient's condition. The prevalence and risk factors of hypersensitivity (HSR) to iodised contrast media were examined in a study by Cha et al.(18) in 196,081 patients. The overall frequency of HSR was 0.73%, of which severe reactions occurred in 0.01% of patients. Logistic analysis showed that the main risk factors for HSR included previous cases of hypersensitivity to ICM, hyperthyroidism, drug allergy, and a family history of HSR. The individual history of hypersensitivity turned out to be particularly substantial (198.8), which indicates the possibility of a genetic predisposition to such reactions. Measures such as premedication with antihistamines (0.5) and changing the type of contrast agent (0.5) were effective in reducing the risk of recurrence of HSR. These results highlight the importance of a preliminary assessment of risk factors for the prevention of hypersensitivity reactions and the use of preventive measures in patients with an increased likelihood of HSR.

In the study by Edelmuth et al.(19), the tolerability and effectiveness of increased doses of intrathecal contrast in lateral decubitus CT myelography (LDCTM) were evaluated to improve the detection of venous fistulas of cerebrospinal fluid. In the group of 24 patients, contrast doses of 10 ml and 20 ml were compared. The results showed that increasing the dose to 20 ml was well tolerated, with no reported moderate or severe side effects. The technical characteristics of LDCTM improved in the group with a higher dosage: the contrast attenuation values on the second side under study were statistically higher compared to the group receiving the standard dose. This indicates that an increased dose of contrast can improve visualisation with LDCTM. However, for the final assessment of safety and diagnostic efficacy, additional studies involving a larger number of patients are required.

The effect of intravenous administration of iodine and gadolinium-based contrast agents on symptoms in patients with myasthenia gravis was examined by Geenen et al.(20). In a sample of three retrospective examinations, including 374 patients with myasthenia gravis who received iodine-containing contrast and 313 patients who underwent non-enhanced CT, an increase in symptoms was observed in 6.1% and 3.5% of patients, respectively. Contradictory data were identified in a detailed analysis: two studies did not find a link between contrast administration and deterioration, whereas one study showed a substantial increase in symptoms within 24 hours after administration of iodine-based contrast (6.3% in the contrast group and 0.6% in the control group). Despite rare cases of exacerbation of symptoms, iodine-based contrast agents can cause an increase in myasthenic symptoms in less than 5% of patients, while gadolinium-containing contrasts agents are recognised as safe for this group.

A multicentre study by Baek et al.(21) evaluated the quality and safety of low-concentration iodinated contrast agents (iohexol, iopamidol, and iodixanol) during cerebral angiography. The study included 243 patients who underwent diagnostic cerebral angiography. The image quality assessment did not reveal substantial differences between the three types of contrast agents, which confirmed their comparability with more highly concentrated agents. Side effects were observed in 28.8% of patients, of whom 27.2% had acute, mostly mild, reactions, and 3.3% – delayed ones. There were no substantial changes in vital signs or electrocardiogram after administration of contrast agents. The study showed that low-concentration iodised contrast agents have a good safety profile and are not inferior in image quality to highly concentrated analogues, which makes them a potentially safer option for patients undergoing cerebral angiography.

The reviewed studies demonstrate that while contrast agents are essential tools in modern diagnostic imaging, their safety, particularly in sequential use for CT and MRI, requires careful consideration. The pharmacokinetics and potential adverse effects of iodine-containing contrast agents highlight the importance of managing intervals between procedures, especially in patients with renal impairment, to minimize the risk of contrast-induced nephropathy. Gadolinium-based contrast agents have shown significant diagnostic benefits but carry concerns regarding gadolinium accumulation, particularly in the central nervous system. The safety of these agents, especially when used in combination or sequentially, underscores the need for rigorous patient monitoring, with particular attention to pre-existing conditions such as kidney disease or allergies. A tailored approach to contrast selection and dosing, considering both the benefits and potential risks, is crucial for enhancing patient safety and improving diagnostic outcomes in clinical practice.

Safety of barium contrast agents in radiology

Other contrast agents, such as barium, are used in radiography to improve visualization of the gastrointestinal tract. Barium sulfate is the most commonly used contrast agent for X-ray examinations, such as barium enema or barium blind passage, as it provides a clear image of the organ walls due to its radiopacity. This enables a thorough assessment of the functional state of organs like the esophagus, stomach, and intestines allowing for the detection of various pathologies such as ulcers, polyps, or tumors. Despite its high effectiveness, barium has some limitations, such as the inability to use it in patients with intestinal perforation or barium allergy.

Contrast agents for ultrasound examinations (US) are gaining popularity due to their safety and

applicability in many clinical cases where ultrasound is used to study organs and blood vessels. US contrasts consist of microscopic gas bubbles that enhance the reflection of ultrasound waves and allow for a more detailed assessment of the structure and function of organs such as the liver, kidneys, or heart. They are used to improve images when studying vascular abnormalities, such as varicose veins, or to assess blood flow in tumors. The natural biocompatibility of such contrast agents and the minimal risk of side effects make them effective and safe for patients, including pregnant women, where other contrast methods may be contraindicated.

Bonilha et al.(22) reported that the modified barium swallow study (MBSS) is a low-dose X-ray method used to diagnose swallowing disorders and assess the risk of aspiration. Recent data have shown that radiation exposure in MBSS is associated with a very low risk of cancer in adult patients. The use of standardized protocols helps to reduce radiation doses without loss of diagnostic accuracy. However, lowering the pulse rate to reduce radiation exposure may impair diagnostic accuracy, making this strategy ineffective. Radiation exposure levels also remain low for children, although the exact cancer risks for this age group are unknown. The main conclusion of the study is that MBSS can be safely used for diagnosis while complying with radiation safety standards, minimising potential risks for patients, both adults and children.

The study by Tipnis et al.(23) evaluated the average radiation dose during a modified barium swallow study (MBSS) in 200 adult patients, with an average dose of 0.32 mSv, classifying it as a low-radiation examination. The study used various projections, allowing clinicians and patients to better assess the radiation risks compared to other sources of exposure. It is essential to adhere to the principle of *as low as reasonably achievable* to minimize potential risks while maintaining the diagnostic value of the procedure.

In contrast, the safety of CT and MRI contrast agents raises specific concerns. When these agents are used sequentially, particularly iodinated agents for CT and gadolinium-based agents for MRI, it is crucial to manage the interval between procedures to reduce the risk of agent accumulation in the body, especially in patients with impaired renal function. Additionally, the potential for allergic reactions and toxic effects must be considered when these agents are used frequently in a series of diagnostic examinations.

The study by Gross et al.(24) highlighted the importance of evaluating the safety of contrast agents, such as barium, used in specific procedures. While barium is commonly used in other imaging studies, its safety during administration must continuously be assessed in the context of a patient's anatomical features. These considerations underscore the need for clear safety protocols for the sequential use of various contrast agents in clinical practice, particularly when multiple procedures, such as CT and MRI, are required within a short time frame.

Goldman et al.(25) examined the safety of modified barium swallow (MBS) procedures in the context of the COVID-19 pandemic, highlighting the increased risk of infection transmission due to coughing and aerosol formation during the procedure. International guidelines have led to the development of safety protocols to minimize infection risks, especially for patients with community-acquired respiratory infections (C-ARI). While these protocols significantly reduce the transmission risk, the study emphasizes the importance of adapting safety measures to ensure the well-being of both patients and healthcare providers. However, when considering sequential imaging procedures involving contrast agents, such as CT and MRI, the potential for compounding risk must be closely monitored, particularly in patients with compromised respiratory or immune systems.

In the study by Barbon et al.(26), the use of liquid barium for videofluoroscopic studies in patients with oropharyngeal cancer post-chemotherapy illustrated its effectiveness in visualizing swallowing dysfunction. Barium provided clear imaging of swallowing processes, highlighting safety concerns related to aspiration risk. Despite its utility in diagnosis, the study underscores the necessity of carefully monitoring the use of contrast agents, such as barium, particularly when multiple diagnostic tests, including CT or MRI, are required in quick succession. In the case of CT and MRI, the safety profile of iodinated and gadolinium-based contrast agents must be assessed in light of the cumulative effect on patient safety when used sequentially. This includes consider-

ations of kidney function, potential for allergic reactions, and the need for adequate intervals between procedures to minimize toxicity or other adverse effects.

In the paper by Schmidt et al.(27), barium paste was used to improve the visualization and planning of the needle trajectory during percutaneous glycerin rhizotomy under CT control. Barium was applied to the patient's skin to clearly identify the surface landmarks and the oval opening of the skull using CT. This allowed a more accurate guide of the spinal needle into the oval hole using a laser localisation system built into the CT scanner. The use of barium provided improved visualisation of important anatomical structures, which increased the accuracy of the procedure and reduced the risk of errors. The use of barium paste, in combination with CT guidance, resulted in a reduction in radiation exposure for both medical personnel and the patient, compared with traditional fluoroscopy techniques. This approach has demonstrated increased safety and effectiveness of the procedure without substantial complications.

The use of contrast agents such as barium, iodine-based agents, and gadolinium-based agents in various imaging procedures presents both benefits and challenges in terms of patient safety. Barium remains a valuable tool in radiography, particularly for gastrointestinal studies, but requires careful consideration of patient-specific factors and potential risks, especially in sequential imaging with other contrast agents like those used in CT and MRI. The safety protocols for barium-based procedures, such as the modified barium swallow study, have been shown to reduce radiation risks, but their use must be closely monitored, particularly in patients with respiratory or immune system concerns. Additionally, when combining iodinated and gadolinium-based agents, careful management of intervals between procedures is essential to minimize cumulative risks, such as kidney damage, allergic reactions, and potential toxicity. As these agents are increasingly used in clinical practice, especially in complex diagnostic pathways, a comprehensive approach to their safety, considering both their individual and combined effects, is critical for optimizing patient outcomes.

Safety of gadolinium-containing contrast agents

Gadolinium-based contrast agents are of substantial value for the diagnosis and monitoring of diseases (28). However, studies have shown that linear non-ionic gadolinium-based macrocyclic contrast agents tend to accumulate in the cerebral cortex and the deep brain structures such as the striatum and dentate nucleus. Linear agents are susceptible to deceleration, which makes them the main culprits of gadolinium accumulation in the central nervous system (CNS). Macrocyclic gadolinium chelates accumulate in lower concentrations, which explains the absence of changes in MRI after repeated use. In this regard, the use of linear gadolinium-containing agents was limited, except a gadoxetic and gadobenic acids. Macrocyclic drugs are recommended, as they are more stable and release gadolinium less frequently. The use of contrasts should be minimised and assigned only when necessary. Concerns about gadolinium toxicity have intensified research into alternative imaging techniques and contrast agents. Patients with multiple sclerosis who frequently undergo MRI are most at risk from gadolinium-based contrast agents (GBCA). Further research is needed to determine whether new MRI techniques without contrast can improve the accuracy of the diagnosis of this disease. Given the uncertainty of the long-term risks of gadolinium deposition and the absence of noticeable symptoms, it is important to carefully assess the risk-benefit ratio when prescribing GBCA, especially in patients with frequent contrast use.

Holowka et al.(29) analyzed the safety of GBCA, emphasizing their effectiveness in MRI while noting concerns about potential side effects. Nephrogenic systemic fibrosis, a serious complication previously associated with GBCA use, has decreased significantly due to guidelines limiting their use in patients with impaired renal function. However, the long-term effects of gadolinium deposition in tissues, particularly in the brain, remain uncertain. This highlights the importance of a cautious approach in prescribing gadolinium-based agents, particularly for patients with hypersensitivity or compromised renal function. When used sequentially with other contrast agents, such as iodinated agents in CT, careful consideration of the cumulative risk, especially in patients with pre-existing conditions, is necessary. Weighing

the risks and benefits of each contrast agent is crucial to avoid unnecessary exposure, particularly when repeated or simultaneous imaging procedures are required.

Loevner et al.(30) demonstrated that the new contrast agent gadopiclenol, at a lower dose of 0.05 mmol/kg, provides comparable diagnostic performance to the standard gadobutrol (0.1 mmol/kg) in imaging the central nervous system. This study showed that gadopiclenol offers an equivalent diagnostic yield while reducing the potential for gadolinium accumulation in tissues. These findings make gadopiclenol a promising option for patients requiring repeated imaging or when minimizing gadolinium retention is a priority. When considering sequential CT and MRI procedures, this lower-dose contrast agent may reduce the risks associated with gadolinium deposition, making it a safer alternative for repeated diagnostic imaging.

In a paper by Mahmood et al.(31), the effect of high-energy radiation on the stability of gadolinium-based contrast agents using hybrid magnetic resonance links was evaluated. Three GBCAs – gadoteric acid, gadobutrol, and gadoxectic acid – were tested in various concentrations to identify possible degradation of the organic ligand and release of toxic gadolinium. The samples were irradiated with a dose of 100 Gy, and T1 relaxation time measurements were performed before and after radiation exposure. The results showed that there were no differences in values between irradiated and non-irradiated samples, indicating the absence of GBCA degradation at clinically applied radiation doses. The established detection limit for free gadolinium was 1-1.5%, which confirmed the high sensitivity of the method. These data support the safety of GBCA use in the context of radiation therapy; however, further in vivo studies are required for definitive conclusions.

Cheeney et al.(32) analyzed the safety of intravenous contrast agents used in MRI, CT, and ultrasound examinations of children. It was noted that contrast agents are generally safe for pediatric patients, but it is important to consider the rare side effects that may occur. Knowing how to prevent and treat such events is vital for minimising risk and improving treatment outcomes. Possible accumulation of gadolinium in tissues requires special attention when discussing with medical specialists and parents. The use of gadolinium-based contrast agents in patients with severe chronic kidney disease (CKD) was examined by Rudnick et al.(33). It has previously been shown that the use of GBCA in such patients can cause nephrogenic systemic fibrosis (NSF). However, due to the restriction on the use of GBCA in patients with CKD and the choice of agents with stronger binding of free gadolinium, cases of NSF have practically disappeared. Current studies demonstrate that the use of GBCA with a high affinity for gadolinium in patients with severe CKD does not cause NSF. Nevertheless, doctors' concerns about the use of these contrasts persist, especially in connection with observations showing gadolinium deposition in brain tissues.

Hama and Tate(34) evaluated the effects of GBCA extravasation in cancer patients, noting that while the incidence of extravasation was low (11 cases out of 16,039 patients), the safety implications were minimal. The extravasated contrast was rapidly cleared from tissues within three days, and no serious consequences were reported. However, this highlights the importance of monitoring for extravasation during contrast agent administration, particularly when multiple diagnostic procedures, such as CT and MRI, are performed sequentially. Although extravasation events are rare, ensuring proper injection techniques and considering potential risks associated with sequential contrast use can help mitigate adverse effects.

Alsogati(35) reviewed the efficacy and safety of gadopiclenol, a newer gadolinium-based contrast agent. The study found that gadopiclenol performed comparably to other GBCAs at lower doses while maintaining high diagnostic accuracy. Importantly, gadopiclenol demonstrated a favorable safety profile, with fewer severe side effects, such as kidney damage, than other agents. This makes gadopiclenol a promising option for reducing the risks associated with gadolinium retention, especially when multiple imaging procedures are required. However, the study noted slight liver retention and prolonged QT intervals, underscoring the need for further research on the long-term effects of gadopiclenol. When considering sequential use of CT and MRI with contrast agents, gadopiclenol may present a safer alternative by reducing gadolinium accumulation in tissues.

Patel et al.(36) focused on the risks associated with the dosage of GBCA during intrathecal administration, emphasizing the dose-dependent

nature of side effects. They found that higher doses of GBCA, particularly above 1.0 mmol, were linked to more severe neurological side effects, including fatal cases of coma. These findings highlight the importance of limiting the dose of gadolinium-based agents, especially in patients who require repeat imaging. When used sequentially with CT, where iodinated contrast agents are commonly used, it is crucial to balance the doses to avoid cumulative toxicity and minimize risks, particularly in patients with pre-existing health conditions, such as kidney disease.

The safety concerns related to nephrogenic systemic fibrosis (NSF) with GBCA use in patients with severe kidney disease have led to the development of safer macrocyclic agents. These newer agents have shown a minimal risk of developing NSF and are now preferred in clinical practice(37,38). This shift has significantly reduced the incidence of NSF. However, despite the ongoing use of GBCA, concerns about gadolinium retention in the body remain, particularly when these agents are used sequentially in patients with kidney dysfunction. This underscores the importance of careful monitoring and patient selection when considering the sequential use of CT and MRI with contrast agents(39).

The use of gadolinium-based contrast agents has always required weighing their clinical benefits and possible risks(40-42). Nephrogenic systemic fibrosis has been associated predominantly with GBCA linear agents, which have led to their limited use, especially in patients with renal insufficiency. The introduction of screening programmes to prevent the use of linear GBCA in vulnerable patients has substantially reduced the incidence of NSF cases. Macrocyclic agents that had higher stability showed an extremely low risk of developing NSF, which made them preferable for clinical use. Screening of patients before the use of macrocyclic GBCA is optional(43-45). Although gadolinium accumulation has been detected in brain tissues, its clinical effects remain unknown, and studies show that macrocyclic agents are gradually eliminated from the body. GBCAs remain important diagnostic tools, helping to prevent serious illnesses and deaths. Ouyang and Bao(39) showed the accumulation of gadolinium in deep brain structures on MRI after the use of GBCA. This was confirmed not only in adults but also in children, which is especially important because of their physiological characteristics. Histological studies on rodents and postmortem analyses of human tissues also demonstrated gadolinium deposition in the brain, bones, and other tissues. Particular attention was paid to comparing the safety of linear and macrocyclic GBCAs in children, as macrocyclic agents demonstrated higher stability and lower risk of accumulation. Based on these data, doctors received practical recommendations that consider the latest achievements in studying the effects of GBCA on the child's body.

While GBCAs are essential tools for MRI diagnostics, concerns regarding their safety, particularly their accumulation in tissues such as the brain, remain significant. The risk of NSF associated with linear gadolinium agents has led to their reduced use, with safer macrocyclic agents being preferred, especially in patients with renal impairments. Newer agents like gadopiclenol offer a promising alternative, showing comparable diagnostic efficacy at lower doses and a more favorable safety profile. However, the potential for gadolinium accumulation, especially in repeated imaging procedures, underscores the importance of careful patient selection and monitoring, particularly in vulnerable groups such as children or patients with chronic kidney disease. When gadolinium agents are used sequentially with other contrast agents, such as iodinated agents in CT, it is crucial to consider the cumulative risk to ensure patient safety.

CONCLUSIONS

The safety of contrast agents, particularly iodine-based agents used in computed tomography and gadolinium-based agents used in magnetic resonance imaging is a critical aspect of modern diagnostic imaging. While these agents significantly enhance diagnostic accuracy, their sequential use poses unique challenges, especially in patients with impaired renal function or pre-existing health conditions. Studies have shown that iodine-containing contrast agents are generally safe when proper intervals between procedures are observed, but careful monitoring of kidney function is essential to prevent contrast-induced nephropa-

thy, particularly during frequent diagnostic examinations.

The use of gadolinium-based contrast agents, while effective for enhancing magnetic resonance imaging, also presents safety concerns, particularly regarding the potential accumulation of gadolinium in the brain and other tissues. Research highlights the importance of limiting exposure, especially in patients with impaired renal function, and preferring macrocyclic agents due to their lower risk of nephrogenic systemic fibrosis and reduced tissue accumulation. Newer agents, such as gadopiclenol, have shown promise in reducing the risks associated with gadolinium retention while maintaining high diagnostic efficacy, making them a safer option for repeated imaging procedures.

Study emphasizes the need for careful patient selection and dose management when using contrast agents sequentially in computed tomography and magnetic resonance imaging, particularly in cases requiring multiple examinations within a short period. The cumulative risk of toxicity, especially in vulnerable populations, requires a comprehensive approach that includes monitoring kidney function, managing allergic reactions, and adjusting contrast agent dosages to minimize adverse effects. As new contrast agents and improved safety protocols continue to emerge, these findings underscore the importance of balancing the diagnostic benefits with patient safety in clinical practice.

The practical significance of this research lies in its ability to guide clinical practice by emphasizing the importance of carefully managing the use of contrast agents in diagnostic imaging, particularly when using iodine-based agents in computed tomography and gadolinium-based agents in magnetic resonance imaging. By understanding the safety profiles, optimal intervals between procedures, and potential risks associated with these agents, healthcare providers can improve patient outcomes by minimizing adverse effects, such as contrast-induced nephropathy and gadolinium retention.

One of the limitations of this study is the potential impact of variations in contrast agent type, concentration, and injection protocols on the reproducibility and reliability of machine learning models. These factors can introduce inconsistencies in the imaging data, influencing the radiomic features extracted for analysis. As a result, the variability in contrast protocols could affect the performance and generalizability of the artificial intelligence models, limiting their ability to provide consistent and accurate diagnostic predictions across different settings.

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Sažetak

Evaluacija sigurnosnog profila kontrastnih sredstava na bazi joda i gadolinija koja se koriste pri CT i MR dijagnostici

M. Z. Lisiecka

Svrha istraživanja bila je ispitati sigurnost kontrastnih sredstava u području medicinske radiologije. Proveli smo sveobuhvatan pregled literature putem baza podataka kao što su PubMed, Google Scholar, Scopus i ScienceDirect, s odabirom relevantnih članaka na temelju ključnih riječi, dizajna studije te objavljivanja na engleskom jeziku razdoblju od 2020. do 2024. godine. Tijekom istraživanja utvrdili smo da se kontrastna sredstva koja sadrže jod često koriste pri medicinskom snimanju, ali njihova sigurnost je zabrinjavajuća, posebno kod pacijenata s oštećenjem bubrega i sklonošću alergijskim reakcijama. Preporučuje se poštivanje intervala od 4-12 sati između postupaka kako bi se smanjio rizik od nefropatije izazvane kontrastom. Jodirana kontrastna sredstva češće uzrokuju nuspojave u usporedbi s kontrastnim sredstvima na bazi gadolinija, ali ozbiljni slučajevi poput anafilaksije su rijetki (0,06%). Kontrastna sredstva niske koncentracije za cerebralnu angiografiju koja sadrže jod pokazala su visoku sigurnost, smanjujući toksične učinke. Barijeva kontrastna sredstva pokazala su visoku razinu sigurnosti kada se koriste u dijagnostici, uključujući postupke poput oralnog testa barijem. Tijekom pandemije COVID-19 posebna se pozornost posvećivala smanjenju izloženosti zračenju i poštivanju sigurnosnih protokola, što je spriječilo širenje infekcija. Sredstva na bazi linearnog gadolinija češće doprinose njegovom taloženju, što bi moglo biti povezano s potencijalnim dugoročnim rizicima, iako njihove kliničke posljedice nisu u potpunosti ispitane. Nasuprot tome, makrociklički kelati gadolinija pokazuju bolju stabilnost i rjeđe uzrokuju takve učinke, što ih čini poželjnijima u kliničkoj praksi. Možemo zaključiti da je uvođenje strogih preporuka o korištenju kontrastnih sredstava koja sadrže gadolinij smanjilo incidenciju nefrogene sistemske fibroze, ali potrebna su daljnja istraživanja o njihovoj akumulaciji u tijelu.

KLJUČNE RIJEČI: *jodirano kontrastno sredstvo, kompjuterizirana tomografija, magnetska rezonancija, gadolinij, barij*