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## Contrast use in image-guided procedures: Balancing Diagnostic Quality and Patient Safety

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### Abstract

*The use of contrast agents in image-guided procedures has significantly improved diagnostic capabilities by enhancing visualization of internal structures, enabling earlier and more accurate detection of pathologies. Contrast medium can be used in different imaging modalities, such as X-rays, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Currently, various types of contrast media are available such as iodine-based, gadolinium-based, barium sulfate agents, microbubbles, and nanoparticles agents. Despite their diagnostic benefits, these agents may lead to serious side effects, posing risks to patient safety and healthcare systems. These adverse effects represent a burden on healthcare systems. The aim of this review is to explore the diagnostic value and adverse effects of contrast media in various settings, and to discuss strategies that can balance contrast use in image-guided procedures diagnostic value with patient safety. Contrast medium has shown effectiveness in diagnosing various diseases including tumors, abscesses, and inflammatory diseases (e.g. Crohn's). However, these agents were linked to multiple side effects, most importantly contrast-induced acute kidney injury and hypersensitivity (early and delayed). A collaborative, multidisciplinary approach involving radiologists, nurses, pharmacists, and allergy specialists should be implemented for optimizing outcomes and minimizing risks.*

**Keywords:** Contrast Agents, Contrast Medium, Contrast Media, Image-Guided Procedures, Diagnostic Value, Patient Safety.

### Introduction

The discovery of X-rays in 1895 by Wilhelm Rontgen has transformed the field of radiology, launching the concept of non-invasive imaging (1). While X-rays rapidly became an essential tool for diagnosing fractures and other bone injuries, the lack of contrast between soft tissues prompted researchers to investigate substances that could image differentiation. The introduction of contrast agents in image-guided procedures has significantly improved the diagnostic capabilities of various imaging modalities (Khattak et al., 2021). Contrast agents can enhance the visualization of internal structures within the body, enabling earlier and more accurate diagnosis of conditions, such as tumors, vascular diseases, and neurological disorders (2).

Contrast agents significantly contribute to enhancing the effectiveness of different imaging

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modalities, such as X-rays, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI). Each modality relies on specific contrast media designed to enhance image clarity and diagnostic accuracy. For instance, iodinated contrast agents are mainly utilized in CT and angiographies (3, 4), while gadolinium-based agents are typically used to enhance MRI images (5). Furthermore, the development of microbubble contrast agents has significantly enhanced ultrasound imaging, leading to more precise, real-time evaluation of blood flow and tissue perfusion (6). Currently, various types of contrast agents are available such as iodine-based, gadolinium-based, barium sulfate, microbubbles, and nanoparticles agents.

Despite their established diagnostic benefits, they bear significant risks that can worsen patient safety. Adverse effects of contrast media include mild hypersensitivity reactions, nephrotoxicity, extravasation, and wide range of rarely reported side effects (7-10). These adverse effects pose significant challenges to clinicians and represent a burden on healthcare systems. Thus, balancing the diagnostic quality of contrast use in image-guided procedures and patient safety is considered a critical manner. The aim of this review is to explore the diagnostic value and adverse effects of contrast media in various settings, highlighting the importance of implementing strategies to balance their diagnostic value with patient safety.

## Methods

A comprehensive literature search was conducted in Medline (via PubMed), Scopus, and Web of Science databases up to April 29, 2025. Medical Subject Headings (MeSH) and relevant free-text keywords were used to identify synonyms. Boolean operators (AND, OR) were applied to combine search terms in alignment with guidance from the Cochrane Handbook for Systematic Reviews of Interventions. Key search terms included: “Contrast”, “Diagnostic Value”, and “Patient Safety”. Summaries and duplicates of the found studies were exported and removed by EndNoteX8. Any study that discusses balancing contrast use in image-guided procedures diagnostic quality and patient safety and published in peer-reviewed journals was included. All languages are included. Full-text articles, case series, and abstracts with the related topics are included. Case reports, comments, animal studies and letters were excluded.

## Discussion

Contrast agents have undergone multiple developments since their discovery in 1895. Initially, various substances such as simple salts (e.g. barium sulfate and potassium bromide) were explored and enhanced tissue contrast but were hindered by toxicity (1). In 1896, Haschek and Lindenthal introduced the first angiogram using a bismuth-based contrast agent (11). A fundamental advancement in the development of iodine-based contrast agents occurred in the 20<sup>th</sup> century (2). Iodine-based contrast agents showed a significant improvement in image quality and lower toxicity, becoming the standard in X-ray imaging (1, 11). Iodopyrine was the first iodine-based contrast agent; it was introduced by Albers-Schonberg in 1906, though with significant side effects (2). Iodine-based contrast agents underwent several subsequent modifications making them safer.

## Types of Contrast Agents

Currently, various types of contrast agents are available:

### *Iodine-Based Contrast Agents*

Iodine-based contrast agents are water-soluble compounds administered intravenously. They contain iodine that can enhance radiodensity and are classified into ionic and nonionic types (11,

12). Nonionic agents, such as ioversol, iohexol, and iodixanol, result in fewer adverse effects due to lower osmolality compared to older ionic agents (13). They act through iodine's high atomic number that leads to strong X-ray absorption, making them effective in CT and angiographic procedures (12). Iodine-based contrast agents are used in contrast-enhanced CT, venography, angiography, VCUG, IVU, and HSG (12, 13). Examples of ionic agents (high-osmolality agents) are diatrizoate sodium/meglumine and iothalamate sodium/meglumine with higher side effects (14), nonionic agents (low-osmolality agents) are iopamidol and iohexol, better for intravascular use, and iso-osmolality agents are iodixanol, that matches serum osmolality with lower toxicity (14).

#### *Gadolinium-Based Contrast Agents*

During the 1980s, MRI imaging showed significant advancement due to the emergence of gadolinium-based contrast agents. These agents improved the detail and clarity of MRI imaging through reducing the relaxation time of water molecules in tissues (5). Gadopentetate dimeglumine (Magnevist) was the first gadolinium-based contrast agent approved for clinical application by the FDA in 1988 (15). To facilitate safe use of MRI, Gadolinium ( $Gd^{3+}$ ) is chelated to mitigate toxicity while keeping its paramagnetic characteristics. It acts through shortening T1 relaxation times, which enhances MRI contrast through accelerating proton realignment following radiofrequency pulse disruption (16). Gadolinium-based contrast agents are mainly used in vascular imaging and detecting blood-brain barrier disruptions (17).

#### *Barium Sulfate Agents*

Barium sulfate ( $BaSO_4$ ) is a non-toxic, insoluble compound derived from barite. It is typically used for gastrointestinal imaging (18), due to its high insolubility and atomic number, causing effective attenuation of X-rays without systemic absorption, making it ideal for enema or oral administration in gastrointestinal studies (18, 19).

#### *Microbubbles Agents*

Microbubbles are spheres filled with gas, shell designed to avoid immune system clearance, made from polymers, albumin, or lipids to enhance stability and lifespan in blood circulation (20). Microbubbles agents are used in ultrasound as echogenic agents, since they reflect sound waves more efficiently, resulting in more detailed visualization of blood flow and perfusion (20, 21).

#### *Nanoparticles Agents*

Nanoparticle agents, currently under extensive investigation, are emerging agents for targeted imaging and therapeutic applications. They were developed to improve MRI clarity, safety, and targeted delivery and include superparamagnetic iron oxide nanoparticles (SPIONs) and gold nanoparticles (AuNPs) (22, 23). SPIONs act through inducing T2 or T2\* relaxation shortening for image contrast, offering an alternative or complementary mechanisms, while AuNPs provide X-ray attenuation and potential for targeted molecular imaging. These agents have better safety, specificity and multifunctionality compared to traditional contrast agents (22-24).

### **Diagnostic Quality of Contrast Media**

Contrast use in image-guided procedures has shown positive results in various settings. Contrast can improve visualization through highlighting specific tissues, organs, or blood vessels. It also helps distinguish between normal and abnormal anatomy (e.g., tumors, clots, inflammation).

Contrast media can be used during interventions like angiography or catheter placement to guide tools and ensure precision. A recent meta-analysis evaluated the diagnostic accuracy of whole heart coronary magnetic resonance angiography (MRA) for detecting significant coronary artery disease; 34 studies were included in this meta-analysis (25). Results showed that MRA has high sensitivity and specificity for detecting significant coronary artery disease with a diagnostic odds ratio of 18.78, indicating a strong association between whole heart coronary MRA results and the actual presence or absence of coronary artery disease (25).

Multiple studies also evaluated the diagnostic value of contrast-enhanced ultrasound (CEUS) in various health issues. A meta-analysis by Liu et al. assessed the efficacy of contrast-enhanced ultrasound in diagnosing sentinel lymph node metastasis in breast cancer (26). The study reported that CEUS has high diagnostic value for sentinel lymph node metastasis in breast cancer with an overall sensitivity of 0.91, specificity of 0.86, and AUC of 0.95. Notably, percutaneous CEUS was more sensitive than intravenous CEUS (26).

Furthermore, a meta-analysis evaluated the ability of CEUS using intravenously administrated microbubble contrast medium to detect active Crohn's disease activity (27). Results of the study showed that the pooled specificity and sensitivity of CEUS were 0.79 (95% CI 0.67–0.88) and 0.94 (95% CI 0.87–0.97), respectively (27). Another meta-analysis evaluated the diagnostic performance of CEUS for thyroid lesions (28). The pooled results indicate that CEUS demonstrated high diagnostic performance for thyroid nodules, with a sensitivity of 0.853, specificity of 0.876, positive likelihood ratio of 5.822, and negative likelihood ratio of 0.195. These results highlighted the strong ability of CEUS to accurately identify both malignant and benign nodules (28).

Contrast medium was also used in CT settings for better diagnosis quality. A recent meta-analysis investigated the diagnostic accuracy of contrast-enhanced CT for neck abscesses (29). The meta-analysis included 23 studies comprising and found that contrast-enhanced CT has pooled a positive predictive value of 0.83 for diagnosing neck abscesses. However, the researchers noted inconsistent diagnostic reliability of contrast-enhanced CT due to considerable overlap between abscesses and cellulitis. They concluded that MRI may offer higher diagnostic accuracy in certain cases (29).

### **Adverse effects of contrast media**

#### *Contrast-induced acute kidney injury*

Contrast-induced acute kidney injury (CI-AKI) was defined in 2002 by the European Society of Urogenital Radiology (ESUR) as an increase in serum creatinine by 44.2  $\mu\text{mol/L}$  or 25% compared with the baseline value within 72 hours following intravascular administration of iodine contrast medium in the absence of surgery, nephrotoxic drugs and other factors (30). In 2011, ESUR Contrast Media Safety Committee guidelines updated the CI-AKI definition to be when renal function is impaired, and serum creatinine content is elevated by 0.5 mg/dL (44.2  $\mu\text{mol/L}$ ) or more than 25% compared with the basic value within 72 hours following intravascular injection of iodine contrast medium, without the influence of nephrotoxic drugs, surgery, and other causes (31). CI-AKI is considered the third leading cause of hospital acquired acute kidney injury (32). Elderly patients and patients with diabetes, basic renal insufficiency, and other adverse factors are at the highest risk of developing CI-AKI (33). CI-AKI incidence in patients with chronic kidney disease is up to 40% (7).

The pathogenesis of CI-AKI is not clear and multiple mechanisms have been introduced to be

involved in the development of CI-AKI, including the production of reactive oxygen species (ROS) and contrast agents-induced direct and indirect effects (34). Regarding direct effects, iodine contrast agents have direct cytotoxic effects on nephrons, including kidney tubular epithelial cells and endothelial cells, resulting in apoptosis, necrosis, interstitial inflammation, mitochondrial dysfunction, and pyroptosis (7). Iodine contrast agents also induce indirect effects by changing the renal hemodynamics, leading to contraction of renal blood vessels and intramedullary ischemia and hypoxia (7). Furthermore, iodine contrast agents may lead to excessive production of ROS or decrease the activity of antioxidant enzymes resulting in elevated inflammatory response and oxidative stress, thus impairing renal function (35). Hypoxia of renal medulla can exacerbate ROS production, resulting in mitochondrial oxidative stress and mitochondrial dysfunction (36). The pathogenesis of CI-AKI is visualized in Figure 1.

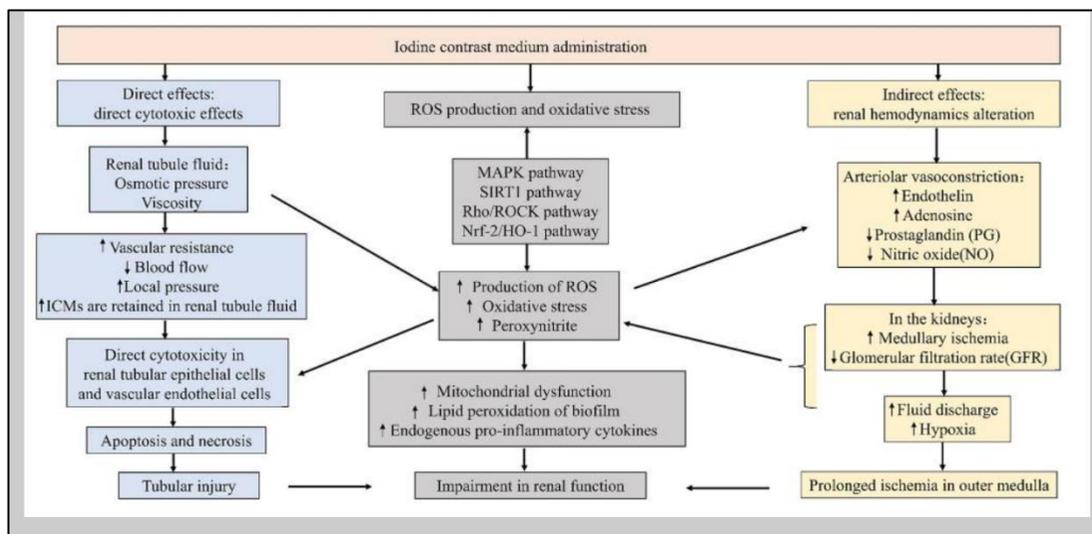


Figure 1. Pathogenesis of CI-AKI (7).

## Hypersensitivity Reactions

Hypersensitivity reactions are observed adverse events of contrast agents using (8). These reactions can be categorized into two classes according to the onset of the reaction in relation to the time of administration: the first type is acute or early reactions that occur within 1 hour of administration, and the second type is delayed reactions that occur between 1 hour and 7 days after administration (37).

### Acute Hypersensitivity Reactions

Acute hypersensitivity reactions severity may manifest by mild cutaneous reactions (such as urticaria or rash) to severe life-threatening reactions such as shock and circulatory collapse (13). This type of reactions is very uncommon, estimated for only 0.6% of all adverse events, with 0.04% classified as severe (13). These reactions are described as allergic-like, anaphylactoid, pseudoallergic, or idiosyncratic reactions (38), because they do not appear to arise from an observable antigen–antibody interaction making their exact pathophysiology unclear. Various pathophysiology processes are believed to be contributing to these early hypersensitivity reactions such as the release of histamine from mast cells and basophils and direct activation of

the complement system (39). Additionally, it was reported that IgE anti-bodies (which are the hallmark of true anaphylaxis) may be another potential mechanism in the hypersensitivity reactions (40).

### **Delayed Reactions**

Delayed reactions are the occurrence of adverse events between 1 hour and 7 days after exposure to contrast media. Reports of the prevalence of delayed reactions due to contrast media exposure varies, incidence rates ranging from 0.52% to 51%, however, most studies showed an incidence below 4% (2). Delayed reactions are mainly mild compared to acute allergic-like reactions and include urticaria, erythema, maculopapular rash, and, rarely, angioedema. The most common delayed cutaneous reactions presentation is macular or maculopapular exanthema. Symmetric drug-related intertriginous and flexural exanthema and drug reaction with eosinophilia and systemic symptoms are specific types of exanthemas commonly associated with delayed skin reactions to contrast media (41).

Pathophysiology of delayed reactions are mainly T-cell mediated as skin biopsies have demonstrated T-cell infiltrate in the dermis (42). History of immunotherapy using recombinant IL-2 agents, history of allergic reactions, and previous reaction to contrast medium are associated with increased risk of contrast-induced delayed reaction (43, 44).

### **Rare Adverse Effects**

Multiple rare adverse effects of contrast agents' exposure were reported by previous studies such as Kounis syndrome, iododerma, leukocytoclastic vasculitis, iodide sialadenitis, and bowel angioedema (10). In addition, intravenous contrast medium extravasation is a significant adverse effect and may vary in severity from minor discomfort to compartment syndrome, skin ulceration, and necrosis. It was also reported that contrast media, particularly iodine-based agents, may have impact on thyroid function. Incidence of contrast-induced thyroid dysfunction ranges from 0.05% to 22% (10).

### **Balancing Diagnostic Quality and Patient Safety**

Jareb et al. introduced a collaborative, multidisciplinary approach involving health administration, radiologists, nurses, pharmacists, and allergists to balance contrast agents diagnostic quality and patient safety (45). Each can uniquely contribute to reducing adverse effects of contrast use in image-guided procedures. Each profession role is summarized in Table 1. Radiologists have a major role to play in enhancing patients' safety by assessing patient risk factors, choosing appropriate contrast agents and dosages, ensuring informed consent, and providing rapid intervention in the event of an adverse reaction using evidence-based protocols (46-49). They also should standardize pre-screening, including patient history and risk stratification, which allows for early identification of high-risk subjects and tailored prophylaxis (50, 51).

Nurses play a frontline role in patient care and are essential to the safe administration of contrast agents. They play a vital role in patient education, screening, monitoring vital signs before, during, and after contrast administration, and responding to emergency situations. Nurses should also observe signs of hypersensitivity, document all relevant clinical data, and administer pre-medication (52-55).

Pharmacists can contribute to patients' safety through educating patients on contrast-related risks, assisting in agent selection, evaluating drug interactions, and designing pre-medication

regimens. They also may contribute to developing and updating institutional protocols and screening tools (39, 56-58).

Allergists are important for identifying high-risk patients and developing personalized desensitization protocols when needed. They assess patients with prior reactions, perform diagnostic skin testing, and design desensitization protocols when necessary. Allergists also can promote ongoing research and quality improvement initiatives aiming to minimize contrast-related hypersensitivity (59, 60).

Interdisciplinary communication is essential for patients' safety. It can be facilitated by shared health records, standardized protocols, team meetings, and simulation training. These efforts support coordinated care and improve outcomes (53, 61). Furthermore, continuing education across disciplines can be effective by ensuring up-to-date practice through workshops, simulation drills, and interdisciplinary learning (46, 57).

Another approach to balance diagnostic quality and patient safety is quality improvement initiatives. These initiatives can involve tracking and analyzing adverse events, refining pre-screening tools, and updating protocols based on data trends. Multidisciplinary review processes and benchmarking also foster a strong safety culture (50, 57).

<b>Radiologists</b>	<p><b>assessing patient risk factors</b>  <b>choosing appropriate contrast agents and dosages</b>  <b>ensuring informed consent</b>  <b>providing rapid intervention in the event of an adverse reaction</b>  <b>using evidence-based protocols (46-48)</b>  <b>standardize pre-screening, including patient history and risk stratification (50)</b></p>
<b>Nurses</b>	<p>patient education  screening, monitoring vital signs before, during, and after contrast administration  responding to emergency situations.  observe signs of hypersensitivity  document all relevant clinical data  administer pre-medication (52, 53)</p>
<b>Pharmacists</b>	<p>educating patients on contrast-related risks  assisting in agent selection  evaluating drug interactions  designing pre-medication regimens.  developing and updating institutional protocols and screening tools (39, 41, 56)</p>
<b>Allergists</b>	<p>assess patients with prior reactions  perform diagnostic skin testing  design desensitization protocols when necessary  promote ongoing research and quality improvement initiatives aiming to minimize contrast-related hypersensitivity (59, 60)</p>
<b>Health administration</b>	<p>Interdisciplinary communication facilitated by shared health records, standardized protocols, team meetings, and simulation training (53, 61)</p>

	continuing education across disciplines up-to-date practice through workshops, simulation drills, and interdisciplinary learning (46, 57) quality improvement initiatives tracking and analyzing adverse events refining pre-screening tools updating protocols based on data trends multidisciplinary review processes and benchmarking (50, 57)
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Table 1.

Roles of different professions in balancing contrast diagnostic quality and patient safety

## Conclusion

Contrast agents play a critical role in improving the diagnostic accuracy of modern image-guided procedures across various settings. Despite their established diagnostic value, their use is not without risk, notably contrast-induced acute kidney injury and hypersensitivity reactions. Balancing diagnostic value with patient safety requires a multidisciplinary approach involving radiologists, nurses, pharmacists, and allergy specialists. Standardized protocols, thorough patient screening, and continuing education are essential to reduce risks. Moving forward, emerging contrast technologies and quality improvement initiatives offer promising avenues to further optimize safety without compromising diagnostic accuracy.

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