

Contrast Agents and Contrast-Induced Nephropathy

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Abstract

Recent advances in medical sciences, especially in imaging, have dramatically increased the use of contrast agents. The constantly changing nature of medicine and the availability of new information, such as new pharmaceutical formulations, have necessitated periodic revisions and drafting of new guidelines for the safe use of intravenous contrast agents in radiology. This study examined the majority of guidelines, articles, and authoritative references available on the use of intravenous contrast agents in adults to reduce the risk of contrast-induced nephropathy. The search engines of PubMed, Web of Science, Scopus, and Google Scholar were used, and relevant English articles cited at least twice between 1979 and 2014 were studied. Review of the collected papers showed no consensus among them for guidelines on the incidence of contrast-induced nephropathy in patients at risk. Different formulas were used to calculate estimated glomerular filtration rate, which could be problematic in some cases. Further studies are needed for unification of existing guidelines.

Keywords

Contrast-Induced Nephropathy, Contrast Agents, Acute Kidney Injury

1. Introduction

Injection of contrast agents is used for computed tomography, body and coronary angiography, interventional radiology and cardiology procedures, and excretory urography. Intravenous contrast agents are divided into three main categories—hyper-osmolar, hypo-osmolar, and iso-osmolar contrast media. Hyper-osmolar contrast

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media are ionic monomers highly hyper-osmolar to plasma (~1400 - 1800 mOsmol/kg). Low-osmolar contrast media are non-ionic monomers with lower osmolarity than hyper-osmolar contrast media but still hyper-osmolar to plasma (~500 - 850 mOsmol/kg). Iso-osmolar contrast media are the most recent non-ionic contrast agents. They involve dimers with an osmolarity of 290 mOsmol/kg. Therefore, these agents have lower osmolarity than the so-called “hypo-osmolar” contrast agents.

Non-ionic hypo-osmolar or iso-osmolar contrast agents are usually five to ten times safer than previous hyper-osmolar types [1]. However, few isolated studies have been conducted on the effects of contrast agents on the kidneys [2]. Some studies have reported a direct or indirect association between contrast agents and the incidence of acute kidney injury (AKI), with an 11% - 14.5% increased risk factor [3]-[5]. Contrast-induced adverse effects are the third cause of AKI after surgery and hypotension at hospitals. The incidence of AKI ranges from 3% to 7% in patients with no risk factors and 50% in patients moderate to advanced chronic kidney disease (CKD) [6].

2. Pathophysiology

The exact cause of contrast-induced nephropathy is not known since hospitalized patients may still show reduced kidney function even when receiving no contrast agents. A retrospective study of 32,161 patients receiving no contrast agents reported a 25% change in creatinine levels in more than half the study population, and a 0.4 mg/dL change in over 40% of patients within 5 days [7].

The available information is related to the study of animal models associated with acute tubular necrosis (ATN) occurrence with two mechanisms of vasoconstriction and direct cytotoxic effects [8]-[16]. However, unlike classic ATN, contrast-induced nephropathy shows a quick recovery and involves a relative sodium excretion (FENa) of less than 1% [17] [18].

Almost all intravenous contrast agents are filtered by glomeruli, and, therefore, blood flow to the renal medulla is reduced because of a change in viscosity. This effect is especially visible in iso-osmolar contrast media [9]. In patients with kidney failure, contrast agents are also secreted through other areas, including the biliary tract or alimentary canal.

Contrast agents in the plasma of people with normal renal function have a half-life of 1 - 2 h. Almost all contrast agents are excreted by the kidneys within 24 h [6]. Most cases of contrast-induced nephropathy are non-oliguric and thus any iodinated contrast materials are dialyzable.

3. Patients at Risk

Clinically significant incidence of nephrotoxicity in healthy people with normal renal function following contrast injection either does not happen or would be extremely rare if reported [19] [20]. To identify patients at risk, measuring only serum creatinine is not enough, and estimation of glomerular ultrafiltration is essential. Serum creatinine levels depend on many factors, and creatinine clearance remains normal until glomerular ultrafiltration is reduced to 50%. The following diseases/conditions can increase the risk of contrast-induced nephropathy [21]-[34] [46]-[49]:

1. A history of kidney impairment or failure, such as surgery, malignancy, dialysis, single kidney, and proteinuria, as the main risk factor, on which there is consensus.
2. Age > 60 - 70 years [33] [34].
3. Use of nephrotoxic drugs and diuretics.
4. Diabetes (simultaneous presence of the disease with renal impairment significantly increases risk).
5. Use of metformin or metformin-like drugs.
6. Hyperuricemia.
7. Hypertension.
8. Congestive heart failure with low left ventricular ejection fraction and New York Heart Association Functional Classification grades 3 - 4.
9. Acute myocardial infarction (>24 h).
10. Intra-aortic balloon pump.
11. Acute hypotension.
12. Sepsis.
13. Dehydration. Contrast agents are not recommended for use in dehydrated individuals of any age, sex, and

physical condition. Being potentially nephrotoxic, they should be avoided if possible [26].

14. A history of chemotherapy.
15. Transplantation.
16. HIV or AIDS.
17. Collagen vascular disease.
18. Multiple myeloma.
19. Low hematocrit.
20. Use of high doses of contrast agents (angiography or computed tomography with repeated injections) at short intervals *i.e.* <24 h. Hypo-osmolar contrast agents have a half-life of 2 h. Approximately 20 h is needed for these materials to be thoroughly removed by the kidneys if they function normally [34]. Therefore, there should be an interval of >24 h between injections if possible.
21. Cirrhosis and liver failure [6].

4. Diagnosis

There are no certain and standard criteria agreed upon among groups working in the field. Various definitions have been proposed, among which, the criterion of the Acute Kidney Injury Network is more comprehensive and acceptable than others. According to the definition provided by this group, AKI is an injury occurring within 48 h of a nephrotoxic incident (e.g. caused by contrast agents) associated with one of the following conditions [35]:

1. An increase of ≥ 0.3 mg/dL in serum creatinine level.
2. An increase of 1.5 times (50%) in serum creatinine level.
3. A decrease of ≤ 0.5 mL/kg/h in urine output for at least 6 h.

It should be mentioned that, usually following injection of contrast agents, serum creatinine levels are enhanced within the first 24 - 72 h but return to initial levels within 14 days [36].

Based on European Society of Urogenital Radiology criteria, contrast-induced nephropathy is defined as an increase of more than 25% or 0.5 mg/dL in the serum creatinine level within 72 h after the injection of contrast material, provided that no other agents can be identified that would increase the serum creatinine level [37].

Urinary sediment can be indicative of classical findings of ATN, incorporating epithelial cell casts and renal tubular cells. However, these findings are not necessary for diagnosis, nor does their absence exclude such diagnosis.

Since many contrast agents cause false-positive results in the detection of urinary protein [38], urine tests for proteinuria should not be performed for at least 24 h following the use of such materials, or tests should be repeated within at least 48 h after their initial application.

In patients with AKI after angiography, contrast-induced nephropathy should be distinguished from atheroembolic renal disease. The latter includes at least one of the following [39]:

1. Simultaneous association of other embolic events such as livedo reticularis.
2. Eosinophilia or transient reduction of complement levels.
3. Delayed injury for several days or weeks.
4. Very low recovery.

Who should be assessed for kidney function prior to injection of contrast agents, and at what intervals should injections be conducted?

Computed tomography does not necessitate serum creatinine measurement for all outpatients receiving contrast injections. Different protocols have been defined at different centers around the world.

All the prestigious English-language guidelines have listed persons at risk of developing kidney damage after contrast injection. However, the guidelines do not agree upon all the afore-mentioned groups. What is accepted by all is that measuring and estimating GFR are necessary for the first seven groups mentioned above as “patients at risk” before intravenous injection of a contrast agent. Nevertheless, creatinine and GFR estimations are essential for any candidate who is undergoing angiography with high doses of arterial injections, especially those listed above as patients at risk [33]-[41].

There is no general consensus on screening intervals (creatinine and eGFR) before contrast studies in the examined guidelines and articles, and the proposed time ranges from 7 days to 6 months. The existing resources suggest this measurement be made for high-risk hospitalized patients 7 days prior to examination [33] [37], though it is possible that it is conducted 30 days before studies for other cases [34].

In cases of emergency where there is no possibility of risk assessment and serum creatinine and eGFR levels are unavailable, necessary measures should be taken to prevent contrast-induced nephropathy. Such measures are discussed below [37].

Different formulas exist for eGFR [Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD)]. It should be noted that the MDRD formula usually underestimates glomerular ultrafiltration compared with other formulas [42] [43], and thus must be used carefully. Using these formulas for amputations and paralysis also of those with exceptional physical conditions (e.g., severe obesity or cachexia) is less reliable and 24-h urine data should be collected to determine creatinine clearance for this group [44].

5. Measures Taken to Reduce Risk

The following measures should be taken to reduce the risk of contrast-induced nephropathy:

1. Use of the lowest possible dose of contrast agent.
2. Use of hypo-osmolar non-ionic monomeric contrast agents or non-ionic dimeric iso-osmolar media [46]. Many centers have stopped using hyper-osmolar agents because of their numerous side effects [34].
3. Use of adequate hydration (oral or intravenous) before and after the procedure.
4. Discontinuation of nephrotoxic drugs 48 h before the procedure.
5. Avoidance of performing contrast studies within 24 h (preferably within 72 h).
6. Performance of dialysis for hemodialysis patients within 24 h after injection. Renal impairment is not generally of concern in these patients, but what could be of concern is the osmotic load caused by the agents, which theoretically could lead to pulmonary edema and anasarca [34].

6. Recommendations for Safe Application of Intravascular Iodinated Contrast Media

The following algorithm is recommended:

- In patients with eGFR > 60 mL/min: the procedure is safe (either IV or IA).
- If 45 mL/min < eGFR < 60 mL/min, IV injection is safe but for IA injection, the patient should be well hydrated and 80% of the maximum dose of IOCM should be administered.
- If 30 mL/min < eGFR < 45 mL/min, IA injection should be avoided and for IV injection, the patient should be well hydrated and 80% of the maximum dose of IOCM should be administered.
- In patients with eGFR < 30 mL/min, intravascular contrast study should be avoided.

[Key: IV: intravenous injections; IA: arterial injections; IOCM: iso-osmolar or hypo-osmolar contrast material]

There is not enough evidence to suggest the existence of an acceptable pharmaceutical treatment currently available in the market (theophyllin, endothelin-1, fenoldopam, N-acetyl-cysteine) to reduce contrast nephropathy [26] [34] [37] [45]. Yet, since N-acetyl-cysteine is not usually associated with many complications, it is still used in some centers. Nonetheless, it must be remembered that screening is not enough before processing and hydration is mandatory using this alternative.

7. Contrast Doses

The standard dose is 2 mL/kg, up to a maximum of 200 mL/kg.

8. Intravenous Contrast agents in the Iranian Market

1. Omnipaque 300 and 350: hyper-osmolar to plasma.
2. Visipaque 320: iso-osmolar with plasma.
3. Ultravist 300: hypo-osmolar.

The precise roles of iso-osmolar agents for the reduction of the risk of contrast-induced nephropathy are not clear. Nevertheless, it is generally accepted that this class of contrast agents produces less discomfort for patients, especially those receiving intra-arterial injections, compared with hypo-osmolar agents.

9. Hydration Guidelines

It is recommended that all patients receive hydrating liquids orally. The three proposed protocols for intravenous

hydration are:

1. Infusion of 0.9% saline or sodium bicarbonate twice the amount of the contrast material [45].
 2. Infusion of 0.9% saline (1 - 1.5 mL/min/h) for 6 h before or after injections, or 3 mL/kg/h and 1 mL/kg/h of sodium bicarbonate (154 mEq/L in dextrose 5%) 6 h before and after injections, respectively [37].
 3. Infusion of 0.9% saline or Ringer's solution (100 mL/min/h) 6 - 12 h before and 4 - 12 h after injections [34].
- Giving liquids to patients with chronic heart failure or those on a limited liquid intake must be avoided.

10. Conclusion

The ever increasing average age of the world's population and enhanced diagnostic procedures requiring injection of contrast agents in patients with chronic renal failure are likely to increase the risk of contrast-induced nephropathy. It is essential that preventive strategies and guidelines in this area are used. The list of people at risk of contrast-enhanced nephropathy is increasing, and there is no consensus among the different schools for treatment protocols. There are many unknown and unsubstantiated points that require explanation about the incidence of contrast-enhanced nephropathy, and further research is required.

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