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Contrast nephropathy; a new look to an old problem

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Abstract

Iodinated contrast media are administered in imaging procedures and may cause acute kidney injury (AKI) which is called contrast-induced nephropathy (CIN) or contrast-associated-AKI (CA-AKI). We searched for relevant articles in PubMed, EMBASE, and DOAJ databases. The most important risk factor for CA-AKI is preexisting renal insufficiency and these patients benefit from administration of low-osmolar contrast media. On the other hand, serum creatinine level is a late indicator of renal function; however, some other biomarkers have been suggested as early indicators of CA-AKI. Furthermore, hydration therapy is the most practical approach to prevent CIN. In this review, we discuss the changes in the contrast materials over the years. We also explore the predictive parameters of developing CIN and its preventive strategies. However, further studies are required to investigate the association between contrast materials and AKI and to find more effective predictive biomarkers and preventive strategies.

Keywords: Contrast induced nephropathy, Prevention, Treatment, Acute kidney injury

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Introduction

Iodine contrast is commonly utilized in diagnostic imaging and therapeutic procedures. One of the complications reported after administering iodinated contrast agents (CA) is acute kidney injury (AKI). AKI is usually reversible but is associated with an increased risk of mortality (1). The type of AKI that occurs after administering CA has been called contrast-induced nephropathy (CIN) for many years; currently, the term contrast-associated-AKI (CA-AKI) is recommended. CA-AKI usually occurs 24-48 hours after the administration of CA with a 25% increase from the baseline serum creatinine level (1,2). The risk of CA-AKI increases by 12% per 100 mL of CA. A previous systematic review showed that comorbidities like diabetes mellitus (DM) and chronic kidney disease (CKD) increase the risk of CA-AKI to 12%-50% compared to individuals without these comorbidities which have a risk of 3.3% to 8% (3).

Results from animal studies show evidence of acute tubular necrosis (ATN) in CIN, but the mechanism is not well-understood (4,5). Two major theories have been reported. The first one involves the direct cytotoxic effects of contrast materials causing ATN. The second theory discusses the ability of the viscosity of contrast materials has in altering nitric oxide (NO) and endothelin balance leading to vasoconstriction and outer medullary hypoxia (4,6,7).

Several animal and uncontrolled human studies consider intravascular iodinated contrasts as nephrotoxic agents (8,9). However, the exact possibility of CI-AKI occurrence is unclear because of the lack of a control group that is not exposed to contrast material in studies as well as coincidental AKI due to hypovolemia, cardiac dysfunction, and infection (9, 10).

In this review, we attempt to answer the following questions; 1) What has changed in the contrast materials over the years? 2) Is there any way to predict the risk of developing CIN? 3) Is it possible to reduce the risk of developing CIN?

Method of search

We searched for articles using the following keywords in the title and abstracts of the articles in PubMed, EMBASE, and DOAJ: prevention, treatment, acute kidney injury and contrast-induced nephropathy.

The transformation of contrast materials

Previously, contrast materials with an osmolality of up to 2200 mOsm/kg had potential biological effects including (11); 1) High-osmolar contrast material shift water from the intracellular compartment to the extracellular compartment and lead to up to 10% hypervolemia and dilution of blood components. 2) Red blood cells (RBCs) that become in contact with high-osmolar contrast agents may lose their water which results in their structural deformity and increased internal viscosity. Consequently, their ability to enter capillaries becomes compromised leading to blocked capillaries with distal tissue anoxia,

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Implication for health policy/practice/research/ medical education

CIN or CA-AKI is a complication of iodinated contrast media administration. The most important risk factor for contrast-associated- AKI is preexisting renal insufficiency and they benefit from using low-osmolar contrast media.

or thrombosis and ischemia. 3) Direct contact of the endothelium with high osmolar materials may cause damage and lead to thrombophlebitis, especially with leg venography. 4) High-osmolar contrast media causes systemic vasodilation in the organs except for the kidney and brain. This leads to uncomfortable flushing and heat sensations in the patients. In the kidney, it can lead to direct toxicity of renal tubular cells and vasoconstriction in the glomeruli (12).

Nowadays, contrast materials are divided into three categories; high-osmolar, low-osmolar, and iso-osmolar. Osmolality is the ratio between the number of iodine atoms and the dissolved particles. Hyperosmolar contrasts with a ratio of 1.5:1, low-osmolar contrast materials with a ratio of 3:1, iso-osmolar material with a ratio of 6:1 have an osmolality of 1000 to 2000 mOsm/kg, 500 to 1000 mOsm/kg, and 290 to 300 mOsm/kg, respectively. The incidence of CIN has decreased since the use of low-osmolar and iso-osmolar contrast materials (13, 14). A study showed that using low-osmolar contrast material significantly reduces the risk of CIN in patients with preexisting renal insufficiency alone or along with diabetes mellitus (15). In addition, a meta-analysis study of 25 trials compared the toxic effects of low-osmolality and high-osmolality contrast media on the kidney. They found that the serum creatinine level increased more in patients with preexisting renal failure that used high-osmolar contrast media compared to those that used low-osmolar contrast media. Therefore, using low-osmolar contrast media seems clinically advantageous in patients with preexisting renal insufficiency (16).

Prediction of contrast-associated acute kidney injury

The most important risk factor for CA-AKI is preexisting renal insufficiency. Therefore, assessing the renal function before the administration of CA is essential. Serum creatinine level is a filtration marker and may be used to assess kidney function. Additionally, the estimated glomerular filtration rate (eGFR), which is calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula, may be used to determine the risk of CA-AKI before administrating intravascular CA (17). The Contrast Medium Safety Committee guidelines of the European Society of Urogenital Radiology recommend preventive measurements in patients with an eGFR <30 mL/min/1.73 m^2 before administrating intra-arterial CA with second-pass renal exposure and intravenous administration and patients with an eGFR<45 mL/min/1.73 m^2 before administrating intra-arterial CA with first-pass renal exposure (17). Other factors that may increase the risk of CA-AKI include chronic heart failure, advanced age, anemia, intravascular volume depletion, the dosage of CA, and nephrotoxic should also be considered (18). Creatinine is a late indicator of renal function and can be affected by different factors such as muscle index, age, gender, diet, arteriosclerosis, and renal tubular secretion (19).

Wang et al compared the alterations in the levels of serum creatinine, serum cystatin C, and eGFR and their ability to early detect CIN in patients undergoing invasive cardiac procedures. The level of serum creatinine was not a useful marker for early detection of CIN. They reported that the alterations in the serum level of cystatin C may be more useful in the early prediction of changes in GFR compared to the serum level of creatinine (20).

In recent years, some biomarkers have been suggested for the early detection of AKI. Urinary renin and angiotensinogen, and neutrophil gelatinase-associated lipocalin (NGAL) have been reported to possibly be able to predict the development of severe AKI. In a study on 99 patients undergoing cardiac surgery, the ratio of urinary angiotensinogen to urinary creatinine (uAnCR) correlated with deteriorating AKI independently from the alterations in the serum creatinine level. In addition, higher levels of uAnCR predicted longer hospital stays, the requirement for kidney transplantation, and worsening AKI (21). A retrospective cohort study on 204 patients who had developed acute kidney injury network (AKIN) stage 1 following cardiac surgery revealed that the combination of urinary levels of angiotensinogen and renin predicted worsening of AKI to severe stages and a mixed outcome of AKIN stage 3 or death (22). In a prospective, cohort study, 616 patients admitted to the emergency department were classified clinically into transient azotemia, AKI, normal kidney function, or stable CKD. Plasma NGAL was measured and was reported to be able to classify the patients into low, moderate, and high categories according to the risk of developing AKI (23).

Preventive strategies

The most cost-efficient and practical approach to avoiding CIN is hydration therapy (24). The hydration mechanism is reported to increase the blood volume and renal infusion, reduce the contrast media (CM) permeability and diuretic impact, inhibit the activation of the renin-angiotensin-aldosterone system (RAAS), and increase vasodilator concentrations, such as NO. Hydration may simultaneously lower CM concentrations in the kidney tubules to prevent direct injury to the epithelial of the kidney tubules by CM (25). Hydration, administered either orally or intravenously, has been reported to be beneficial in avoiding the occurrence of CIN (26). However, since intravenous hydration is measurable it seems more clinically suitable than oral hydration. Currently, it is has

been reported that high-risk patients without signs of heart failure should receive 1 mL/kg/h saline 6–12 hours before and 12–24 hours after the contrast administration (27).

Alkalization therapy has been reported to decrease the occurrence of CIN by increasing the concentration of sodium bicarbonate in the renal tubules, limiting tubule and medulla acidification, neutralizing oxygen free radicals, and, eventually, maintaining renal function (28). Both sodium citrate and sodium bicarbonate were observed to significantly minimize CIN morbidity in patients undergoing coronary angiography and percutaneous coronary intervention (29). However, it has been reported that alkalization with sodium bicarbonate reduced contrast-induced renal impairment more effectively compared to hydration with saline (30). Other investigations have shown no advantage of sodium bicarbonate alkalization over isotonic saline in preventing CIN (31). It is hypothesized that hydration and alkalization have varying preventative benefits for people with varying underlying illnesses, and additional research into their indications is warranted.

Vitamin C (also known as ascorbic acid) is an antioxidant that has been reported to decrease kidney impairment caused by various types of triggers. For example, ascorbic acid scavenges the oxygen free radicals that cause necrosis in conditions such as myocardial infarction. In addition, it also prevents ischemic renal cell death in the renal tubule as an antioxidant (32). Prophylaxis with oral ascorbic acid (oral dose of 3 g at least 2 hours before the procedure and 2 g the night and morning following the procedure) may lower the incidence of CIN in patients with preexisting renal failure that undergo cardiac procedures (33).

Conclusion

In conclusion, CIN or CA-AKI is a complication of CA administration. The most important risk factor for CA-AKI is preexisting renal insufficiency and they benefit from using low-osmolar contrast media. Although serum creatinine level is a late indicator of renal function which can be affected by many factors, some other biomarkers have been suggested as early indicators of CA-AKI. On the other hand, hydration therapy is the most practical approach to prevent CIN. However, other therapies such as alkalization therapy and prophylaxis with oral ascorbic acid (vitamin C) have been reported to be effective in the prevention of CIN as well. Further studies are required to investigate the association between contrast materials and AKI and to find more effective predictive biomarkers and preventive strategies.

Authors' contribution

AP and FK wrote the draft. SH conducted the English and scientific edit. All authors read and signed the final draft.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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