

Contrast-induced Nephropathy

Essentials and Concerns

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The administration of radiocontrast media may lead to kidney injury, known as contrast-induced nephropathy, which is reversible in most cases, but its development may be associated with adverse outcomes. This review article provides recommendations for the prevention of contrast nephropathy.

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INTRODUCTION

Iodinated contrast-enhanced computed tomographic scans or angiographies are done frequently in current medicine, making iodinated contrast medium one of the inevitably prescribed agents in diagnosis of diseases. Intravenous contrast material is used to enhance tissue conspicuity and to expand the diagnostic ability and accuracy. This benefit should be taken into account in addition to the risk of using intravenous iodinated contrast, especially in patients with preexisting renal insufficiency, associated with development of acute kidney injury, known as contrast-induced nephropathy (CIN).¹

A lack of consensus exists concerning the definition and treatment of CIN. In this review article, we take a look at CIN definition, the risk factors and latest accepted therapeutic options in patients undergoing an imaging examination with intravenous contrast medium.

DEFINITION

Contrast-induced nephropathy is the impairment of kidney function defined by Parfrey and Barret in 1994 and measured as 25% increase in serum creatinine from baseline or a 0.5 mg/dL (44 μ mol/L) increase in serum creatinine value within 48 to 72 hours after intravenous contrast administration. In the most recent studies, either absolute 0.3 mg/dL to 0.5 mg/dL increase in serum creatinine or 25% to 50% increase from baseline value has been considered as CIN.² The American College

of Radiology has recommended that the Acute Kidney Injury Network classification be used to define CIN, although those criteria are not designed for this type of kidney failure,³ based on which kidney failure happens when at least one of the following scenarios exists⁴: a 0.3-mg/dL absolute rise in serum creatinine level or greater from baseline value, a 50% relative rise in serum creatinine level or greater from baseline value, and a decrease urine output to less than 0.5 mL/kg/h for at least 6 hours.

RISK FACTORS

Patient-related Factors

Many factors make a patient more susceptible to CIN including: preexisting chronic kidney disease, older age, diabetes mellitus, metabolic syndrome, hypertension, multiple myeloma, advanced heart failure, anemia, hypoalbuminemia, dehydration, recent hypotension, hyperuricemia, history of collagen-vascular disease, chemotherapy, transplantation, concomitant use of metformin, and use of diuretics or nonsteroidal anti-inflammatory drugs. Among the mentioned risk factors, chronic kidney disease is the most important and commonest risk factor of CIN.⁵

Procedure-related Factors

In the case of intra-arterial injection, such as coronary artery angiography, there is a higher risk of nephropathy than intravenous injection. Administration of contrast agents in emergency

cases and injection for therapeutic measures also increase the risk of CIN.^{6,7}

Contrast agent- related Factors

The amount of contrast agent used has been studied as a risk factor for CIN in various studies.⁸ The standard dose based on different resources varies between 2 mL/kg and 200 mL/kg. It has been shown that the risk of developing nephropathy is low in patients who receive less than 100 mL of contrast agent, and the risk of kidney dysfunction increases with increasing volume of consumption.⁹ One study found that among very high-risk patients for CIN, the risk of nephropathy was 4.4% following coronary angiography, when 14 ± 4 mL of contrast medium was used, whereas this could reach to 29.8% in case of prescribing 61 ± 12 mL of contrast agent.¹⁰ It seems that the amount of contrast agent is a key factor in preventing kidney dysfunction in susceptible patients. In different studies, the maximum radiographic contrast dose has been calculated as follows: for each kg of body weight, 5 mL of contrast agent should be considered (maximum 300 mL), and this should be divided by serum creatinine level (mg/dL).

Liu and his colleagues used the contrast medium ratio of volume to estimated glomerular filtration rate as a predictor of CIN after coronary intervention and reported that a ratio of 2.39 and greater could independently predict the risk of CIN after percutaneous intervention in patients with myocardial infarction.¹¹ This should be taken into account that in diabetic patients with a serum creatinine level of 5 mg/dL or greater, using even 20 mL to 30 mL of contrast agent can cause nephropathy. Regarding that performing ventriculography during coronary angiography needs the use of a high amount of contrast medium, it is recommended that ventriculography be avoided and the required information be obtained through alternative methods.

In addition to the amount of contrast, the type of the used contrast medium itself also impacts the development of nephropathy. The contrast agents are classified according to the following specifications: being ionic molecule or nonionic, molecular structure (being monomeric or dimeric), and osmolality. Contrast agents can be categorized into 3 groups of high, low, and iso osmolality (1500 mOsm/kg to 1800 mOsm/kg, 500 mOsm/

kg to 900 mOsm/kg, and around 290 mOsm/kg, respectively).

Ionic-monomeric compounds were used in 1950 for the first time as the first generation of contrast agents; they have high osmolality and their use is limited to extravascular radiology such as cystography. The ionic-dimeric group has a low osmolality of about 600 mOsm/kg.

The nonionic-monomeric category is referred to as the second generation of contrast media since 1980. Osmolality is low (500 mOsm/kg to 900 mOsm/kg); however, this is 2 to 3 times higher than plasma osmolality. Iohexol and iopamidol are among the compounds of this group. The nonionic-dimeric group has lower osmolality levels than the low-osmolality agent; their osmolality is equivalent to the plasma and cause the least complication. Iodixanol is the prominent compound in this group.

In a meta-analysis of 36 randomized controlled trials (7166 patients), From and colleagues showed that iodixanol produced no significant reduction in CIN incidence ($P = .11$). However analysis of patient subgroups disclosed that there was a significant advantage of iodixanol when compared with iohexol alone (odds ratio, 0.25; 95% confidence interval, 0.11 to 0.55; $P < .001$), but not when compared with low-osmolality agents other than iohexol or with other ionic dimers.¹² In a multicenter randomized clinical trial designed to compare the renal effects of iodixanol versus iopamidol, in 526 subjects, results showed that the overall rate of CIN in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures was 10.5%, and there was no significant difference between iodixanol and iopamidol in either peak increase in serum creatinine or risk of CIN.¹³

Considering the studies in this area, iodixanol seems superior to iohexol in diabetics with chronic kidney disease, but there is no more benefit from iodixanol compared with other nonionic contrast agents with lower osmolality. There is a need for stronger studies to compare usefulness of iodixanol with that of low-osmolality agents.

PATHOGENESIS

Pathophysiology of CIN is not fully understood. At rest, nearly 25% of cardiac output reaches the kidneys, most of which refers to the cortex; blood circulation in medulla is limited. It seems

that medullary hypoxic damage plays a key role in developing CIN. The most susceptible part of medulla to hypoxia is deep external medulla, which included metabolically active thick ascending limb of the loop of Henle. Increased viscosity may lead to greater increased tubular interstitial pressure and decreased medullary circulation. In fact, the hemodynamic response to intra-arterial injection of contrast agents seems to be biphasic. Initially, there is an increase in renal plasma flow, glomerular filtration rate, and urine output, which is directly related to the osmolality of the contrast agent. The more the osmolality of used contrast agent, the greater plasma flow rate would be. Due to increased osmotic load and also effect of increased endothelin production, more sodium is reabsorbed by tubular cells, which itself increases the consumption of oxygen. Following an increase in plasma flow transiently, a decrease in renal plasma flow rate in ranges from 10% to 25% would happen over a long period of time. The decrease in blood flow rate seems to be the effect of vasoactive mediators produced by contrast agents. Vasodilators involved in this process include adenosine, nitric oxide, atrial natriuretic peptide, and prostaglandin E2.

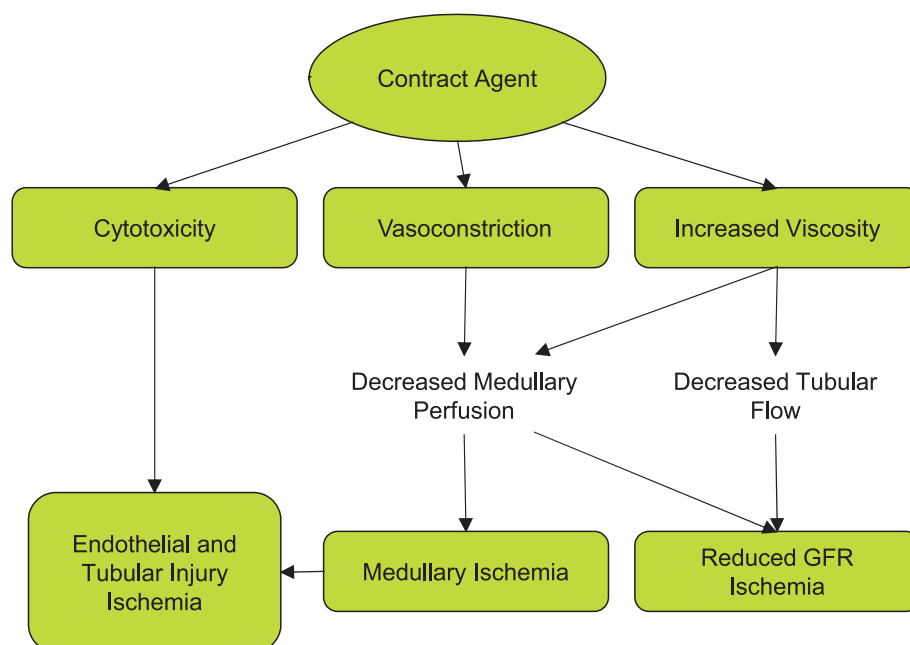
Produced vasoconstrictors are vasopressin, angiotensin II, and endothelin. An imbalance between vasoconstrictor and vasodilator mediators is involved in the pathogenesis of contrast

nephropathy. Apart from the hemodynamic effects of the contrast, which is involved in the pathogenesis of nephropathy, these agents contribute to direct toxic effects on renal tubular cells. These cytotoxic effects include apoptosis, disposition of membranous proteins, decreased extracellular calcium, DNA fragmentation, loss of intercellular connections, disorders in cellular proliferation, and mitochondrial dysfunction. Furthermore, increased production of reactive oxygen species due to reduced blood flow and increased oxygen consumption in the medulla are involved in pathogenesis of CIN.

In summary, contrast agents with effects on the three pathways, reactive oxygen species production, hemodynamic injury, and renal tubular cell injury, induce contrast nephropathy (Figure).¹⁴

DIAGNOSIS

As indicated previously in the introduction, CIN is defined as a 25% increase in serum creatinine level from baseline or a 0.5 mg/dL (44 μmol/L) increase in serum creatinine value within 48 to 72 hours after intravenous contrast administration. Many biomarkers including neutrophil gelatinase-associated lipocalin, cystatin C, urinary kidney injury molecule-1, and interleukin-18 have been suggested for fast detection of CIN; however, they are still in research stage, and their use as



Different mechanisms through which contrast agents may induce contrast nephropathy.

a precise diagnostic method has not been proven yet. Urinary sediment can be consistent with the classic findings of acute tubular necrosis including epithelial cell casts, renal tubular cells, and muddy brown granular casts. However, these findings are not indispensable for diagnosis and their absence also cannot exclude this diagnosis.

It is necessary to mention that following the consumption of contrast agent, false proteinuria may be diagnosed (either with dipstick or sulfosalicylic acid test); therefore, at least until 24 hours after using any contrast agents, checking proteinuria in urine would be worthless. Urine osmolality in these patients tends to be less than 350 mOsm/kg; on the other hand, fractional excretion of sodium, unlike kidney failure due to ischemic and nephrotoxic acute tubular necrosis, is less than 1.

In kidney biopsy, toxic effects of contrast agents on renal tubular epithelial cells are obvious as vacuolization, interstitial inflammation, cellular necrosis, and sometimes, ischemic nephrosis. However, due to the short duration of kidney failure after exposure to the contrast agents and the rapidity of renal recovery, the diagnostic value of renal biopsy in these cases is excluding other causes of kidney failure.

PREVENTION

Contrast-induced nephropathy preventive strategies are summarized in the Table. In 2014, the European Society of Cardiology published a guideline on nephropathy prevention. According to this guideline, all patients who are candidates for receiving contrast agents should be evaluated for risk factors.¹⁵ It is necessary to check the status of kidney function based on one of the determining glomerular filtration formulas such as the Modification of Diet in Renal Disease. In

Preventive Strategies for Contrast-induced Nephropathy

Preventive Strategy
Hydration with normal saline, bicarbonate, or both
Use of N-acetylcysteine
Discontinuation of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, and nonsteroidal anti-inflammatory drugs
Prescription of statins, ascorbic acid, and theophylline
Use of contrast agents with low osmolality or nonionic iso-osmolal agents
Limited contrast agent volume
Hemofiltration or hemodialysis

case of abnormal glomerular filtration rate, the indications of using contrast agents should be revised carefully, and if possible, an alternative imaging method should be replaced or in the lack of suitable substitution, preventive measures should be addressed. In prevention of CIN, the following points should be taken into consideration:

Type and Amount of Contrast Agent

According to various guidelines, it is recommended to use iso-osmolar or low-osmolar agents. While, iso-osmolar agent preference over low osmolars seems to be logical, as mentioned earlier, the superiority of iso-osmolar agents have not been shown in all studies. It is recommended that iodixanol or other non-ionic low-osmolar compounds such as iopamidol or ioversol be used instead of iohexol. Also as stated earlier, the minimum required amount of contrast agent should be used and if there is a need to repeat the procedure, at least 48 hours should pass from previous administration.

Adequate Hydration

It seems that the most effective way to prevent nephropathy is to have adequate hydration before the procedure. In low-risk patients, oral consumption of liquids may be sufficient (though there are different opinions regarding the oral use of fluids); however, in patients with moderate or high risk or in patients who are admitted, hydration with intravascular crystalloid solutions is the preferred mode of hydration.¹⁶ Compared with normal saline (0.9%), it seems that sodium bicarbonate (1.26%) may be a better preventive solution as bicarbonate itself is reactive oxygen species scavenger and can turn urine to an alkaline fluid furthermore lack of chloride (which has vasoconstrictive properties) gives it the better preventive effect.

In a clinical trial in 2016, 100 patients with kidney dysfunction (estimated glomerular filtration rate ≤ 60 mL/min/1.73 m) who underwent elective or emergent coronary angiography were enrolled in the study and assigned randomly to treatment with sodium bicarbonate solution using either the short regimen (intravenous bolus 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 1 hour immediately before contrast agent) or the long regimen (initial intravenous bolus of 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 6

hours).¹⁷ Data indicated that there was a significant increase in serum creatinine level, and a decrease in estimated glomerular filtration rate 48 hours postintervention in short regimen group compared with long regimen group specified that the long regimen of bicarbonate supplementation was a more effective strategy to prevent CIN than the short regimen. Final results showed that hydration with sodium bicarbonate was associated with a significant decrease in CIN among patients with preexisting renal insufficiency (odds ratio, 0.67, 95% confidence interval, 0.47 to 0.96; $P = .03$); nevertheless, it could not decrease the risks of dialysis and mortality and consequently cannot improve the clinical prognosis of patients with CIN.¹⁸ Considering all these studies, it cannot be definitely said that sodium bicarbonate is superior to normal saline, because some studies have shown this superiority and other studies have found equivalent risk of nephropathy in both groups. On the other hand, from the economic point of view, consuming normal saline seems cost effective and does not have problems with the preparation of bicarbonate serum. What is recommended in terms of fluid therapy are as follows: in outpatient settings, intravenous 3 mL/kg/h of any previously mentioned solutions for 1 hour immediately before contrast agent and 1 mL/kg/h to 1.5 mL/kg/h during the administration of contrast up to 4 to 6 hours after that (6 mL/kg/h in total after consumption of contrast agent); and in inpatient settings, 1 mL/kg/h of any previously mentioned solutions for 6 to 12 hours before using contrast agent, during and 6 to 12 hours after the end of administration.

Using mannitol for prevention of nephropathy is not recommended. Regarding oral hydration, some studies have shown that use of salt-free solutions did not affect the CIN compared with isotonic saline; however, other studies have found comparable effects of oral salt and water solutions with intravenous normal saline.¹⁹ In 2017, Matsunami and coworkers compared oral rehydration solution with saline infusion for prevention of CIN in rats. They showed that hydration with saline could only prevent the rise in plasma creatinine in comparison with oral rehydration solution, which prevented increased both plasma creatinine and blood urea nitrogen, and made creatinine clearance better.²⁰ In the latest meta-analysis published in 2018, 4

studies (538 cases) were included for evaluation of oral hydration efficacy in prevention of CIN after coronary angiography or intervention. Data showed the noninferiority of oral hydration in comparison with intravenous hydration in patients either with no kidney dysfunction or patients with mild-to-moderate kidney failure after angiography or angioplasty.²¹

N-Acetyl-L-Cysteine

This medication is an inexpensive combination that is well tolerated. It has both antioxidant and vasodilatory effects. In fact, this is an acetyl cysteine amino acid, which becomes a strong antioxidant and a suitable scavenger for oxygen free radicals by the sulfhydryl group. N-acetyl-cysteine can also amplify vasodilator effects of nitric oxide. Several different studies have been conducted to clarify the exact effects of N-acetyl-cysteine, and results have shown that using 600 mg of this drug before contrast exposure would be effective in reducing the incidence of CIN. It must be mentioned that meta-analysis still could not come into a single recommendation possibly because of heterogeneity in different recruited studies. In summary, some studies have shown a 50% reduction in the incidence of nephropathy with using N-acetyl-cysteine, while others have considered the role of this drug insignificant.²² In 2017, a meta-analysis of total 19 previous studies was performed to evaluate the effectiveness of N-acetyl-cysteine in prevention of CIN in patients after coronary intervention. The results showed that using this drug orally is not as effective as what we thought to prevent CIN.²³ In another recent randomized clinical trial in Greece, intravenous administration of N-acetyl-cysteine could not reduce CIN in critically ill patients after contrast-enhanced computed tomography.²⁴

A most recent meta-analysis, published in February 2018, included the results of 107 previously published studies and showed that using statin plus N-acetyl-cysteine accompanying with intravenous saline is the most effective treatment for the prevention of CIN after coronary angiography.²⁵

Regarding the recommended dose of N-acetyl-cysteine, studies are also different. A group of studies found no significant difference between 600 mg twice daily compared with 1200 mg twice a day, while a meta-analysis on 1677 cases showed a lower risk of nephropathy in high-dose group.²⁶

The European Society of Cardiology guidelines recommended that N-acetyl-cysteine should not be used alone and infusion of standard fluids should be maintained simultaneously.²⁷

Statins

The logic behind the use of statins in preventing CIN is the effect of these drugs on reducing oxidative stress and inflammation accompanying with improvement of endothelial function. A meta-analysis showed that among patients undergoing coronary percutaneous intervention, the use of short-term statins decreased the incidence of CIN, and hence, is highly recommended even in patients with low levels of low-density lipoprotein cholesterol.²⁸ Another updated meta-analysis demonstrated that preprocedural rosuvastatin treatment could significantly reduce the incidence of CIN in patients undergoing cardiac catheterization. However, rosuvastatin treatment did not seem to be effective for preventing CIN in chronic kidney disease patients undergoing elective cardiac catheterization.²⁹ Other studies show the efficacy of further statins included atorvastatin and pravastatin; however, it seems that we still do not have enough evidence to support the use of statins alone in prevention of CIN.

Ascorbic Acid

A comparison between the effect of ascorbic acid and N-acetyl cysteine has not shown a significant benefit; however, these studies were not strong enough. In 2016 in a meta-analysis conducted on 8 randomized clinical trials, results showed that the greatest reduction in CIN was seen with N-acetyl-cysteine plus intravenous saline and ascorbic acid could not add any extra benefit.³⁰

Hemodialysis and Hemofiltration

Contrast agent is basically excreted through glomerular filtration; therefore, in patients with kidney failure the elimination of substance would be slowed down. On the other hand, in one session of dialysis, 60% to 90% of contrast agent is taken. Theoretically, these procedures are expected to be beneficial in reducing nephropathy, but we still face a lot of controversies. In short, there is no consistent recommendation for hemodialysis or hemofiltration as a routine practice in patients who receive contrast media.

CONFLICT OF INTEREST

None declared.

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