Contrast-Induced Nephropathy: What We Know, What We Think We Know, and What We Don't Know

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ABSTRACT

Contrast-induced nephropathy is a common but poorly understood problem. A large body of literature devoted to the subject is replete with contradictions and conflicting reports. The purpose of this article is to summarize our current understanding of the problem by reviewing some of the best studies done to date. Recommendations based on the current literature are also provided.

KEYWORDS: Contrast, nephropathy, contrast-induced nephropathy, review, renal insufficiency, radiology

Objectives: Upon completion of this article, the reader will understand the risks associated with intravenous contrast and strategies to prevent radiocontrast-induced nephropathy.

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Despite being one of the most common causes of acute renal failure in hospitalized patients, contrast-induced nephropathy (CIN) is a poorly understood problem. A great deal of research has been devoted to the subject, and the mechanism of CIN has been explored in countless animal and clinical trials. Many protocols to prevent CIN have been established with varying degrees of success. Some, such as preprocedural hydration, have become “standards of care” that are nearly universally used. Others were fashionable for short periods of time before being discredited. Sadly, some protocols designed to protect the kidneys have been found to do just the opposite. The purpose of this article is to provide a practical overview of the current

knowledge of CIN by reviewing some of the best trials done to date. This article does not present an extensive discussion of the molecular basis of contrast nephropathy or attempt to explain proposed mechanisms of prophylactic drug pharmacokinetics. This review is intended to provide clinicians with a short, practical guide to this problem.

WHAT IS CONTRAST NEPHROPATHY?

Contrast nephropathy is iatrogenic induction of renal impairment after administration of contrast media. A > 25% increase in serum creatinine or rise of > 0.5 mg/dL in serum creatinine within 3 days of contrast medium

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administration is generally considered “contrast-induced nephropathy.”

What We Know

PEOPLE WITH RENAL IMPAIRMENT ARE MORE SUSCEPTIBLE TO CONTRAST-INDUCED RENAL FAILURE THAN PATIENTS WITH NORMAL RENAL FUNCTION

In patients with normal renal function, the incidence of significant CIN is very low (<2%). In patients with preexisting renal insufficiency, it is a significant problem.^{1,2} Although a plethora of disorders may lead to renal failure, once renal insufficiency exists (creatinine > 2 mg/dL), all patients are predisposed to CIN and the relative risks of CIN are similar irrespective of the underlying etiology of renal insufficiency. Other risk factors for CIN include diabetes mellitus, congestive heart failure, volume depletion, repeated contrast administration within 72 hours, and nephrotoxic drugs. Interestingly, multiple myeloma, which has long been considered a risk factor for CIN, may not increase risk when these patients are well hydrated and have normal renal function.³

THE MORTALITY RATE OF PATIENTS WITH CIN IS SEVERALFOLD HIGHER THAN THAT OF MATCHED CONTROLS WITHOUT CIN

One study found that development of CIN increases mortality by up to 30-fold.¹ In this study of 1826 patients undergoing coronary interventions, renal failure without need for dialysis developed in 14.5% of patients and 0.7% required dialysis. Diabetic patients with acute renal failure had greater than 30-fold increased in-hospital mortality compared with patients with similar risk factors who did not develop renal failure.

HIGH-OSMOLAR CONTRAST MATERIAL IS MORE NEPHROTOXIC THAN LOW-OSMOLAR OR ISO-OSMOLAR CONTRAST MATERIAL

Despite some evidence to the contrary, it is generally well-established that nonionic low-osmolar contrast material is less nephrotoxic than ionic contrast material. In the Iohexol Cooperative Study, 1196 patients were randomly assigned to receive ionic or nonionic contrast material.⁴ All patients also received preprocedure prophylactic hydration. Patients with renal insufficiency receiving ionic contrast material were 3.3 times as likely to develop acute nephrotoxicity as those receiving non-ionic contrast material. A meta-analysis performed by Barrett and Carlisle reached similar conclusions.⁵

PREPROCEDURAL HYDRATION WITH 0.9% NORMAL SALINE IS PROTECTIVE AGAINST CONTRAST-INDUCED RENAL FAILURE

Hydration is unequivocally protective against CIN. Conversely, dehydration increases the risk of CIN. From the theoretical point of view, prehydration may

decrease activity in the renin-angiotensin system, augment diuresis and sodium excretion, and dilute contrast media, among other things. In many studies published to date, hydration has been the control arm of investigations using diuretics, vasodilators, calcium channel blockers, or dopaminergic agents. Almost invariably, hydration was found to be as effective as or more effective than the hydration plus other agents.⁶⁻⁸ One study also suggested that with respect to preprocedural hydration, 0.9% normal saline is superior to 0.45% normal saline.⁹ In this report, 1620 patients received isotonic ($n = 809$) or half-isotonic ($n = 811$) hydration. CIN was significantly reduced with isotonic (0.7) versus half-isotonic (2.0%) hydration ($p = 0.04$).

FENOLDOPAM IS NO MORE PROTECTIVE AGAINST CIN THAN PREPROCEDURAL HYDRATION

Fenoldopam showed early promise as an agent that could reduce the risk of CIN. However, two well-designed studies disproved its effectiveness. The multicenter, randomized, double-blind CONTRAST trial studied 315 patients with renal insufficiency undergoing cardiac procedures.⁷ Patients were randomly assigned to receive either fenoldopam or placebo. CIN occurred in 30.1% of patients in the placebo group compared with 33.6% of patients in the fenoldopam group. An additional study by Allaqaband et al had similar results.¹⁰ Besides the apparent ineffectiveness, other disadvantages of fenoldopam have made it inconvenient and militated against widespread acceptance. These include the necessity of intravenous infusion, the need to titrate dose on the basis of blood pressure, and the incidence of serious hypotension in a small minority of patients.

GADOLINIUM IN LOW DOSES (0.3 MMOL/KG) IS NOT NEPHROTOXIC TO MOST PATIENTS BUT ITS ROLE IN CIN REMAINS UNDEFINED

When gadolinium is given in small doses (0.3 mmol/kg or less), it is rarely nephrotoxic. Numerous studies have documented its use in digital subtraction angiography.¹¹⁻¹⁴ However, its utility as an alternative contrast agent for this purpose has faced scrutiny. At doses higher than 0.3 mmol/kg, nephrotoxicity has been reported.¹⁵ Therefore, using high doses (> 40 mL) is not recommended. Gadolinium is also costly and, at equivalent x-ray attenuation, more nephrotoxic than iodinated contrast media.¹⁶ Thus, the lack of nephrotoxicity demonstrated in some studies may have been attributable to the low dose of contrast medium used rather than the inherent properties of the agent itself. Finally, gadolinium is not approved by the Food and Drug Administration for intra-arterial administration.

CARBON DIOXIDE IS NOT NEPHROTOXIC

Carbon dioxide is an invisible, odorless gas that has great utility as a contrast agent in vascular and interventional

radiology. It is not nephrotoxic,^{17,18} although it does have unpleasant symptoms in some patients such as nausea and pain with injection. Its limitations include its unsuitability for cerebral, neck, or spinal angiography and the facts that a power injector is not available in the United States and proper utilization of this agent requires training.

THE LOWER THE DOSE OF CONTRAST MEDIUM, THE LOWER THE RISK OF CIN

The risk of CIN is clearly dose dependent.^{1,3,19} One useful formula that can provide a general guideline regarding the upper limit of contrast volume administration is:

$$\text{Weight (kg)} \times 5 / \text{serum creatinine (mg/dL)}^{19}$$

Thus, a 70-kg man with a serum creatinine level of 2 mg/dL can receive up to 175 mL of contrast material. In a large study of 1826 patients undergoing coronary angiography, 100 mL was found to be the cutoff dose below which there was no CIN requiring dialysis.¹ However, CIN has been reported at very low doses. Therefore, the lowest possible dose should always be used.

PERIPROCEDURAL HEMOFILTRATION IS RENAL PROTECTIVE; PROPHYLACTIC HEMODIALYSIS IS NOT

Hemodialysis can effectively remove all water-soluble contrast media from the body. Unfortunately, studies to date have shown that it does not protect against CIN.^{20,21} This is thought to be due to the fact that renal injury occurs very rapidly after administration of contrast material. Thus, by the time hemodialysis is instituted, it is already too late.

Hemofiltration is a continuous renal replacement therapy whereby ultrafiltrate production is matched by isotonic fluid replacement. No net fluid loss or overload occurs. Marenzi et al randomly assigned 114 consecutive patients with chronic renal failure undergoing coronary interventions to hemofiltration or isotonic saline hydration.²² CIN occurred less frequently among the patients in the hemofiltration group than among the control patients (5% versus 50%, $p < 0.001$). Temporary hemodialysis or hemofiltration was required in 25% of the control patients and in 3% of the patients in the hemofiltration group. The rate of in-hospital events was 9% in the hemofiltration group and 52% in the control group ($p < 0.001$). In-hospital mortality was 2% in the hemofiltration group and 14% in the control group ($p = 0.02$), and the cumulative 1-year mortality was 10% and 30%, respectively ($p = 0.01$). The drawbacks of this technique include high cost and invasive treatment settings. Nonetheless, this strategy merits consideration given the high costs, morbidity, and mortality incurred by patients with CIN.

What We Think We Know

PREPROCEDURAL HYDRATION WITH SODIUM BICARBONATE IS SUPERIOR TO HYDRATION WITH 0.9% NORMAL SALINE

One report suggested that sodium bicarbonate may be more effective than normal saline in preventing CIN.²³ A prospective, single-center, randomized trial involving 119 patients with stable serum creatinine levels of at least 1.1 mg/dL were randomly assigned to receive a 154 mEq/L infusion of either sodium chloride (as a bolus of 3 mL/kg per hour for 1 hour before iopamidol contrast followed by an infusion of 1 mL/kg per hour for 6 hours after the procedure) or sodium bicarbonate (similar protocol) before and after contrast administration. CIN occurred in eight patients (13.6%) infused with sodium chloride but in only one (1.7%) who received sodium bicarbonate. A follow-up registry of 191 consecutive patients receiving prophylactic sodium bicarbonate and meeting the same inclusion criteria as the study resulted in 3 cases of CIN (1.6%). The authors concluded that hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of contrast-induced renal failure. Further studies are needed to validate these results.

FUROSEMIDE AND MANNITOL MAY INCREASE THE RISK OF CIN

Although there have been many studies comparing administration of various potentially renal protective drugs, to the author's knowledge, only two controlled randomized studies compared hydration, mannitol, and furosemide.^{6,24} In the first investigation, 78 patients with chronic renal insufficiency who underwent cardiac angiography were randomly assigned to receive 0.45% saline alone for 12 hours before and 12 hours after angiography, saline plus mannitol, or saline plus furosemide. Among the 28 patients in the saline group, 3 (11%) had an increase in serum creatinine, as compared with 7 of 25 in the mannitol group (28%) and 10 of 25 in the furosemide group (40%) ($p = 0.05$). One report, the Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study, had differing results.²⁴ In this prospective, randomized, controlled, single-blind trial, 98 participants were randomly assigned to forced diuresis with intravenous crystalloid, furosemide, mannitol (if pulmonary capillary wedge pressure < 20 mm Hg), and low-dose dopamine versus intravenous crystalloid and matching placebos. Two participants in the experimental arm versus five in the control arm required dialysis. The authors concluded that forced diuresis with intravenous crystalloid, furosemide, and mannitol, if hemodynamics permit, beginning at the start of angiography provides a modest benefit against CIN provided a high urine flow rate can be achieved.

What We Don't Know

N-ACETYLCYSTEINE IS PROTECTIVE AGAINST CIN

In 2000, Tepel and colleagues published a study showing that *N*-acetylcysteine given twice orally (600 mg) the day before and after administration of contrast medium along with intravenous hydration decreased the incidence of CIN by more than 10-fold (2% versus 21%).²⁵ Several additional studies published soon after demonstrated similar results.^{26,27} Unfortunately, several newer studies have cast some doubt on initial published reports.

Briguori et al randomly assigned 183 consecutive patients with impairment of renal function, undergoing coronary and/or peripheral angiography and/or angioplasty, to receive 0.45% saline intravenously and acetylcysteine (600 mg orally twice daily; group A, $n = 92$) or 0.45% saline intravenously alone (group B, $n = 91$) before and after nonionic, low-osmolality contrast dye administration.²⁸ In the subgroup with a low (< 140 mL) contrast dose, renal function deterioration occurred in 5 (8.5%) of 60 patients in the saline-alone group and in 0 of 60 patients in the acetylcysteine group ($p = 0.02$). In the subgroup with a high contrast dose, no difference was found (5 of 31 versus 6 of 32 patients, $p = 0.78$). Therefore, acetylcysteine appeared to be of benefit only when lower doses of contrast material were administered. Additional well-designed, randomized studies also did not support the utility of *N*-acetylcysteine, nor did they find benefit even at lower doses.^{29–31}

Conflicting studies led Birck et al to perform a meta-analysis of seven randomized trials including 805 patients.³² They found that compared with periprocedural hydration alone, administration of acetylcysteine and hydration significantly reduced the relative risk of contrast nephropathy by 56% ($p = 0.02$) in patients with chronic renal insufficiency. No significant relationship was identified between the relative risk of contrast nephropathy and the volume of contrast medium administered or the degree of chronic renal insufficiency before the procedure. A second meta-analysis performed by Nallamothu et al studied 20 trials involving 2195 patients and concluded that acetylcysteine may reduce the incidence of contrast-related nephropathy, but this finding is reported inconsistently across currently available trials.³³ A third meta-analysis of prospective controlled trials noted that research on *N*-acetylcysteine and the incidence of radiocontrast nephropathy is too inconsistent at present to warrant a conclusion on efficacy or a recommendation for its routine use.³⁴ Overall, this question is unanswered, and several trials are under way to define further the role of acetylcysteine in prevention of CIN.

ISO-OSMOLAR CONTRAST MEDIUM IS LEAST NEPHROTOXIC AMONG ALL CONTRAST AGENTS

Two studies have suggested that iso-osmolar contrast medium may be less nephrotoxic than low-osmolar

contrast medium.^{35,36} Aspelin and associates³⁵ conducted a randomized, double-blind, prospective, multicenter study including 129 patients comparing the nephrotoxic effects of an iso-osmolar, dimeric, nonionic contrast medium (iodixanol) with those of a low-osmolar, nonionic, monomeric contrast medium (iohexol). The creatinine concentration increased significantly less in patients who received the iso-osmolar contrast agent. No patient receiving iodixanol had an increase of 1.0 mg per deciliter or more, but 10 patients in the iohexol group (15%) did. The mean change in the creatinine concentration from day 0 to day 7 was 0.07 mg per deciliter in the iso-osmolar group and 0.24 mg per deciliter in the low-osmolar group ($p = 0.003$). The researchers concluded that CIN may be less likely to develop in high-risk patients when iso-osmolar contrast medium is used rather than a low-osmolar, nonionic contrast medium. However, several other studies have not replicated these results.^{7,26,37} For instance, in their study of fenoldopam, Stone et al reported that one third of patients who received iso-osmolar contrast material sustained CIN versus one fourth of patients who received low-osmolar contrast material.⁷

OVERALL RECOMMENDATIONS

When employing a strategy to prevent CIN, I think several considerations should be made. First, do no harm. If current data do not strongly support use of a prophylactic agent that could be deleterious (e.g., furosemide), do not administer it. Second, be liberal with drugs that may help prevent CIN if they have no significant adverse effects (e.g., using sodium bicarbonate, iso-osmolar contrast material, or *N*-acetylcysteine). On the basis of the previous discussion, the following recommendations can be made regarding patients with renal insufficiency:

1. Avoid contrast material in patients whenever possible.
2. Use alternative contrast studies (e.g., magnetic resonance angiography) or agents (e.g., carbon dioxide) when possible.
3. In patients who must receive contrast material,
 - a. Administer preprocedural intravenous hydration such as sodium bicarbonate as a bolus of 3 mL/kg per hour for 1 hour before contrast followed by an infusion of 1 mL/kg body weight per hour for 6 hours after the procedure.
 - b. Consider *N*-acetylcysteine administration (600 mg by mouth twice a day) the day before contrast administration.
 - c. Use iso-osmolar contrast material.
 - d. Always use the lowest dose of contrast material possible.

- e. If hemofiltration is available, consider using it, especially in patients with poor function and multiple risk factors.

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