Chapter 32. Prevention of Contrast-Induced Nephropathy

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Background

Radiocontrast-induced nephropathy (RCIN) represents an increasingly common cause of treatment-related renal failure[1-3] and increases mortality independent of other risk factors.[4] Major risk factors for RCIN include chronic renal insufficiency,[2,3,5] diabetes mellitus[2,3,5] (especially when accompanied by renal insufficiency[1]), any condition associated with decreased effective circulating volume,[6] and use of large doses of contrast media.[2,3,5,6]

For at-risk patients, clinicians must use their judgment to determine if imaging modalities that do not involve contrast media are an acceptable alternative to contrast studies. In many cases, however, such alternatives do not exist. Moreover, RCIN occurs in patients without obvious risk factors. Thus, strategies for reducing the incidence of RCIN include not just risk factor identification, but modification of these risk factors, choice of contrast media less likely to cause RCIN, and administration of therapeutic agents that further reduce the risk of RCIN.

Practice Description

The specific practices reviewed in this chapter are:

- *Use of high versus low osmolar iodinated contrast media to prevent RCIN.[7]*

- *Use of a standard intravenous or oral hydration protocol for patients with risk factors for RCIN.[8-10]* Typical intravenous protocols evaluated consist of normal saline administered at 75 mL/hr beginning at 12 hours before and ending 12 hours after the procedure. Oral protocols require ingestion of 1000 mL of water during the 10 hours prior to the procedure, followed by intravenous normal saline at 300 mL/h for 30-60 minutes and continued for a total of 6 hours after the procedure.

- *Use of a standard hydration protocol supplemented by pretreatment with theophylline[11-15]* (various doses and schedules)

- *Use of a standard hydration protocol supplemented by pretreatment with N-acetylcysteine[16]* (600 mg bid one day before and day of procedure)

Single studies evaluating atrial natriuretic peptide, prostaglandin E1[17] and captopril[18] were not reviewed, as the data are too preliminary, despite findings that suggest a reduction in the risk of RCIN. Although the evidence supporting the use of N-acetylcysteine largely comes from a single study as well, we do review this practice because the study was large, published in a prominent journal, and has received considerable attention among clinicians.[16]

The use of calcium channel blockers in preventing RCIN was not evaluated, as the existing literature predominantly indicates the practice is ineffective.[19-23]

Prevalence and Severity of the Target Safety Problem

While definitions of RCIN vary, most study definitions include a 25% increase in serum creatinine (SCr) and/or at least a 0.5 mg/dL increase in SCr within 48 hours of contrast administration. Using this definition, one large community-based study of 1826 patients undergoing invasive cardiac procedures reported a rate of RCIN of 14.5%.[2] A controlled prospective study of the onset of RCIN after contrast-enhanced brain CT found an incidence of 2.1% in low-risk patients without diabetes mellitus or chronic renal insufficiency versus 1.3% in a similar control group that did not receive any contrast (p=NS).[24] In comparison, patients in a prospective controlled study undertaken to determine the risk of nephrotoxicity from contrast radiography in patients with diabetes and renal insufficiency (SCr >1.7mg/dL) found a 9% incidence of RCIN.[1]

The cumulative effect of multiple risk factors increasing the risk of RCIN was demonstrated in one uncontrolled study that evaluated the effect of 5 factors (contrast volume >200 mL, albumin <3.5 g/L, diabetes, serum sodium <135 mmol/l, SCr>1.5 mg/dL).[3] When all risk factors were present the risk of RCIN was 100%, compared with just 1.2% when none were present. While most patients with RCIN suffer little morbidity and recover to near baseline renal function within 7-10 days (and thus we characterize it as a Level 2 outcome), rare patients require temporary dialysis. Two studies suggested that the development of RCIN may lead to longer lengths of stay[8,11] and one large retrospective study showed that hospitalized patients who develop RCIN had a mortality rate of 34% compared with 7% in control subjects, even after controlling for underlying co-morbidities.[4] The development of RCIN appeared to increase the risk of death from non-renal causes such as sepsis, bleeding, respiratory failure and delirium.

Opportunities for Impact

Few studies have rigorously evaluated current practice patterns among radiologists or cardiologists with respect to evaluation of a patient's threshold creatinine prior to ordering contrast procedures. One survey study of academic and private practice radiology departments found that only about 20% of practices routinely obtain serum creatinine levels before contrast administration.[25] Interestingly, when patients were known to have a high-risk condition like diabetes, approximately 60% of the same practices would require a serum creatinine before contrast administration. Therefore, many high-risk patients are not identified prior to undergoing contrast radiography studies. In addition, no studies have evaluated the frequency with which physicians recommend pre-hydration for patients prior to contrast studies. Overall, physicians and institutions do not follow a consistent practice in screening patients for risk factors for RCIN prior to the use of contrast radiography. If rigorous evidence identifies patients at risk for RCIN, and effective, standardized preventative measures are developed and implemented, there is substantial opportunity to reduce morbidity.

Study Designs

The literature on strategies for preventing RCIN includes: one meta-analysis evaluating the nephrotoxicity of high versus low-osmolality iodinated contrast media,[7] one randomized controlled study of pre-treatment with acetylcysteine[16] for high-risk patients, one randomized controlled trial of pre-treatment with prostaglandin E1[17] for high-risk patients, and 5 randomized controlled trials assessing the impact of theophylline[11-15] in preventing RCIN. Unfortunately, each of the studies of theophylline employed different routes and dosages (and, in fact, one of

the studies used aminophylline, rather than theophylline). Table 32.1 summarizes the salient features of these studies.

One randomized trial compared inpatient versus outpatient hydration regimens,[26] but we found no randomized controlled trial that evaluated pre-hydration versus no hydration. Thus, support for the standard use of pre-hydration to prevent RCIN is extrapolated from randomized controlled studies of saline versus saline *plus* additional pre-treatment agents like mannitol, furosemide and dopamine[8-10] and smaller observational studies[6,27,28] evaluating the benefits of pre-hydration.

Study Outcomes

Studies evaluated Level 2 outcomes, primarily by measuring changes in serum creatinine, creatinine clearance or glomerular filtration, and assessing the frequency of developing acute renal failure after radiocontrast infusions. Most studies defined RCIN as a 25% increase in creatinine and/or at least a 0.5 mg/dL increase in serum creatinine within 48 hours of contrast administration.

Evidence for Effectiveness of the Practice

All of these studies (Table 32.1) evaluated the effects of various prophylactic measures to reduce the incidence of RCIN. Use of low-osmolar contrast media was supported by one large meta-analysis [7] that compared low versus high osmolar contrast media. Low osmolar contrast media was found to be less nephrotoxic than high osmolar contrast media, with an odds ratio for RCIN of 0.61. Among patients with baseline renal insufficiency (SCr >1.4 mg/dL) the odds ratio of developing RCIN was 0.5 if low osmolar instead of high osmolar contrast media was used.

As previously noted, no randomized controlled trials have evaluated the efficacy of pre-hydration versus no pre-hydration. Data from 3 randomized controlled trials[8-10] using pre-hydration versus other pre-treatments *and* pre-hydration revealed that pre-hydration alone was equivalent to pre-hydration and low dose dopamine or mannitol,[8] and, in one study, superior to pre-hydration and furosemide.[10] The incidence of RCIN in patients with SCr >1.6 mg/dL or creatinine clearance <60 mg/min treated with pre-hydration alone undergoing cardiac catheterization was 11%; excluding the patients with SCr >3 mg/dL, the incidence was only 4%.[8] One retrospective, observational study of high-risk patients undergoing cardiac catheterization supports the benefit of pre-hydration (>500 mL of 0.9% NS in the pre-catheterization period, p• 0.01) in reducing RCIN.[6] In addition, 2 observational studies without controls[27,28] showed that pre-hydration in high-risk patients was associated with low rates of RCIN, although one of these studies[27] used a stricter definition for RCIN (increase in BUN by 50% or 20 mg/dL, and/or increase in SCr of 1 mg/dL within 24 hours).

A recent study of the oral antioxidant acetylcysteine in combination with pre-hydration in high-risk patients with renal insufficiency showed significant protective effect against RCIN versus pre-hydration plus placebo.[16] This protective effect appeared to be even more significant among patients with more advanced renal dysfunction and SCr >2.5 mg/dL. The overall relative risk reduction of 90% observed in this study is so large that it raises the possibility of some sort of bias or other explanation for the observed results. Additional studies of this practice would be valuable, despite the safety and low cost of N-acetylcysteine.

Studies employing theophylline are more controversial. Three randomized control trials showed a significant protective effect of various dosages and administration routes of theophylline among low-risk patients with relatively normal baseline renal function.[12-14] All 3 studies showed theophylline to be protective against a decrease in glomerular filtration rate

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(GFR) or creatinine clearance (CrCl) after contrast administration. On the other hand, 2 studies conducted in high-risk patients with renal dysfunction showed no effect for theophylline in reducing RCIN.[11, 15] Thus, insufficient evidence supports the use of theophylline as prophylaxis against RCIN in high-risk patients.

Potential for Harm

The impact of a system to identify high-risk patients prior to contrast radiography and implement aggressive prophylactic measures to reduce the incidence of RCIN has not been studied. While most patients will not experience any harm from contrast, the potential for "harm" due to delayed or cancelled investigations may be greater than the harm prevented by screening for risk factors, aggressive hydration, or use of particular pre-treatment regimens.

Costs and Implementation

At least 4 studies have evaluated the cost-effectiveness of low-osmolality versus high-osmolality contrast media.[29-32] In all 4 studies, the selective use of low-osmolar contrast media was more cost-effective than its universal use because of the overall small benefits were outweighed by the considerable increased institutional costs. Alternatively, a standardized system to identify high-risk patients and implement the simple prophylactic treatment of pre-hydration would diminish the frequency of the target problem. It would require collaboration between the patients' own physician and the personnel performing the particular contrast study (radiology department, radiologist, diagnostic/interventional cardiologist). This type of intervention could be implemented as part of a hospital-based pathway (see Chapter 52) targeted at reducing radiocontrast-induced nephropathy.

There are no cost-effectiveness or feasibility studies that evaluate protocols for aggressive identification of high-risk patients undergoing contrast radiography and utilization of standardized hydration protocols to reduce RCIN. Two studies suggest most patients with normal renal function (SCr <1.7 mg/dL) can be easily identified by simple questionnaire, resulting in significant cost savings from a reduction in the number of routine serum creatinine levels obtained prior to imaging.[33,34] The cost-effectiveness of using pharmacologic pre-treatment with N-acetylcysteine or theophylline has not been studied.

Comment

In summary, patients with multiple risk factors for RCIN who need radiography with contrast media should receive pre-hydration and low osmolar iodinated contrast. Overall, there appears to be indirect evidence that RCIN can be attenuated by pre-hydrating high-risk patients. Clearly, the use of low osmolar contrast media is associated with less RCIN, but its high cost militates against routine use in all patients. We believe that it should continue to be reserved for the patient with multiple risk factors for RCIN. While newer pre-treatment regimens like N-acetylcysteine, prostaglandin E1, and captopril look very promising in preventing RCIN, these results need to be replicated in further studies. Finally, many institutions would benefit from a hospital-based pathway that identifies patients with multiple risk factors for RCIN prior to contrast radiography. Guidelines (Chapter 51) for appropriate pre-hydration and the timely use of low osmolar contrast media to reduce the development of RCIN would be beneficial.

Table 32.1. Studies of strategies for preventing radiocontrast-induced nephropathy (RCIN)*

Study Setting	Study Design, Outcomes	Results
Low osmolar contrast media		
Meta-analysis of the relative nephrotoxicity of high (HOCM) vs. low (LOCM) osmolar iodinated contrast media[7]	Level 1A, Level 2	LOCM less nephrotoxic than HOCM; pooled p=0.02 Odds of ARF with LOCM 0.61 times that of HOCM (95% CI: 0.48-0.77). Patients with RF at baseline, odds of ARF were 0.5 (CI: 0.36-0.68).
Pre-hydration plus diuresis		
Patients with SCr >1.8mg/dL randomized to IVF, IVF + furosemide, IVF + furosemide + low dose IV dopamine +/- mannitol (if post-cardiac catheterization, PCWP <20 mmHg)[9]	Level 1, Level 2	No differences in rates of renal failure between groups. Rates of RCIN 21.6% if UOP >150 mL/h, 45.9% if UOP <150 mL/h.
Patients with SCr >1.6mg/dL or CrCl <60mL/min randomized to IVF, IVF + mannitol or furosemide pre-cardiac catheterization[8]	Level 1, Level 2	No statistically significant difference in RCIN, among the three groups. After exclusion of patients with SCr >3 mg/dL, RCIN in patients with IVF alone 4%, IVF + mannitol 24% (p=0.02), IVF + furosemide 25% (p=0.02). LOS increased by 4 days in RCIN group.
Patients with SCr >1.7 or CrCl <60mL/min randomized to IVF + furosemide vs. discretion of treating physician during contrast radiography[10]	Level 1, Level 2	SCr increased by 0.42 mg/dL +/- 0.20 treatment group vs. 0.023 mg/dL +/- 0.073 (p<0.01) controls. Significant weight loss in treatment group vs. controls (p<0.03)
Observational study of "high risk" patients with SCr >1.9 mg/dL who underwent cardiac cath[6]	Level 3, Level 2	Statistically significant risk factors for RCIN: volume of contrast used (168+/- 11 vs. 122+/16 mL, p=0.001) and use of prehydration (>500mL 0.9% normal saline in preceding 24 hrs, p<0.01)

Table 32.1. Studies of strategies for preventing radiocontrast-induced nephropathy (cont.)*

Study Setting	Study Design, Outcomes	Results
N-Acetylcysteine		
Patients with SCr >1.2 mg/dL or CrCl <50 mL/min randomized to pre-hydration (IVF) with oral acetylcysteine or placebo prior to contrast CT[16]	Level 1, Level 2	RCIN developed in 2% treatment group vs. 21% control group (p=0.01). Among patients with SCr >2.5 mg/dL, RCIN 0% treatment vs. 42% controls (p=0.02)
Theophylline		
Patients randomized to theophylline (165mg IV x 1) vs. placebo prior to contrast radiography.[12]	Level 1, Level 2	GFR reduced 85.4 +/- 3.8 mL/min controls vs. 107 +/-3.6 mL/min treatment group (p• 0.001).
Patients randomized to theophylline (2.8 mg/kg orally q12 x 2 days) vs. placebo prior to contrast radiography with LOCM or HOCM.[13]	Level 1, Level 2	CrCl after LOCM decreased by ~18% at 24 hrs in control (p<0.05) vs. no significant change over 48 hrs in treatment group. CrCl after HOCM decreased by ~40% at 24 hrs and remained low at 48 hrs in controls (p<0.01) vs. ~24% at 24/48 hrs in the treatment groups (p<0.05). CrCl after HOCM significantly lower in control vs. treatment group (p<0.01).
Patients randomized to pre-hydration + theophylline (5mg/kd IV) or placebo prior to contrast CT or DSA.[14]	Level 1, Level 2	GFR decreased at 4 hrs and 2 days in placebo (88 +/- 40 to 75 +/- 20 mL/min, 89+/- 41 mL/min to 66+/- 32 mL/min, p<0.01) with no significant change in CrCl in the treatment group.
Patients with SCr >1.5mg/dL randomized to pre-hydration vs. pre-hydration with low dose dopamine or aminophylline prior to cardiac catheterization.[11]	Level 1, Level 2	Overall incidence of RCIN was 38%. No significant differences were noted among the groups. LOS was longer in patients with RCIN (7.1 days vs. 3.1 days, p=0.02).
Patients randomized to pre-hydration + theophylline (270 mg q am/540 mg q pm 2d before, 3d after) or placebo prior to contrast CT or DSA.[15]	Level 1, Level 2	No significant differences in SCr or CrCl between groups (RCIN 3.4% controls, 5.7% in treatment, p=NS).

* ARF indicates acute renal failure; CI, confidence interval; CrCl, creatinine clearance; CT, computed tomography scan; DSA, digital subtraction angiography; GFR, glomerular filtration rate; IVF, intravenous fluids; LOS, length of stay; NS, not statistically significant; PCWP, pulmonary capillary wedge pressure; SCr, serum creatinine; and UOP, urine output.

References

1. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med*. 1989;320:143-149.
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368-375.
3. Rich MW, Crecelius CA. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. *Arch Intern Med*. 1990;150:1237-1242.
4. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *JAMA*. 1996;275:1489-1494.
5. Lautin EM, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. *AJR Am J Roentgenol*. 1991;157:49-58.
6. Brown RS, Ransil B, Clark BA. Prehydration protects against contrast nephropathy in high risk patients undergoing cardiac catheterization. *J Am Soc Neprhol*. 1990;1:330A.
7. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology*. 1993;188:171-178.
8. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:1416-1420.
9. Stevens MA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido-Allen DA, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol*. 1999;33:403-411.
10. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron*. 1992;62:413-415.
11. Abizaid AS, Clark CE, Mintz GS, Dosa S, Popma JJ, Pichard AD, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol*. 1999;83:260-263, A5.
12. Kolonko A, Wiecek A, Kokot F. The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. *J Nephrol*. 1998;11:151-156.
13. Katholi RE, Taylor GJ, McCann WP, Woods WT, Jr., Womack KA, McCoy CD, et al. Nephrotoxicity from contrast media: attenuation with theophylline. *Radiology*. 1995;195:17-22.
14. Erley CM, Duda SH, Schlepckow S, Koehler J, Huppert PE, Strohmaier WL, et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. *Kidney Int*. 1994;45:1425-1431.
15. Erley CM, Duda SH, Rehfuss D, Scholtes B, Bock J, Muller C, et al. Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. *Nephrol Dial Transplant*. 1999;14:1146-1149.

16. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180-184.
17. Koch JA, Plum J, Grabensee B, Modder U. Prostaglandin E1: a new agent for the prevention of renal dysfunction in high risk patients caused by radiocontrast media? PGE1 Study Group. *Nephrol Dial Transplant*. 2000;15:43-49.
18. Gupta RK, Kapoor A, Tewari S, Sinha N, Sharma RK. Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. *Indian Heart J*. 1999;51:521-526.
19. Seyss C, Foote EF. Calcium-channel blockers for prophylaxis of radiocontrast-associated nephrotoxicity. *Ann Pharmacother*. 1995;29:187-188.
20. Khoury Z, Schlicht JR, Como J, Karschner JK, Shapiro AP, Mook WJ, et al. The effect of prophylactic nifedipine on renal function in patients administered contrast media. *Pharmacotherapy*. 1995;15:59-65.
21. Russo D, Testa A, Della Volpe L, Sansone G. Randomised prospective study on renal effects of two different contrast media in humans: protective role of a calcium channel blocker. *Nephron*. 1990;55:254-257.
22. Neumayer HH, Junge W, Kufner A, Wenning A. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial. *Nephrol Dial Transplant*. 1989;4:1030-1036.
23. Cacoub P, Deray G, Baumelou A, Jacobs C. No evidence for protective effects of nifedipine against radiocontrast-induced acute renal failure. *Clin Nephrol*. 1988;29:215-216.
24. Cramer BC, Parfrey PS, Hutchinson TA, Baran D, Melanson DM, Ethier RE, et al. Renal function following infusion of radiologic contrast material. A prospective controlled study. *Arch Intern Med*. 1985;145:87-89.
25. Lee JK, Warshauer DM, Bush WH, Jr., McClennan BL, Choyke PL. Determination of serum creatinine level before intravenous administration of iodinated contrast medium. A survey. *Invest Radiol*. 1995;30:700-705.
26. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest*. 1998;114:1570-1574.
27. Eisenberg RL, Bank WO, Hedgcock MW. Renal failure after major angiography. *Am J Med*. 1980;68:43-46.
28. Teruel JL, Marcen R, Herrero JA, Felipe C, Ortuno J. An easy and effective procedure to prevent radiocontrast agent nephrotoxicity in high-risk patients. *Nephron*. 1989;51:282.
29. Barrett BJ, Parfrey PS, Foley RN, Detsky AS. An economic analysis of strategies for the use of contrast media for diagnostic cardiac catheterization. *Med Decis Making*. 1994;14:325-335.
30. Michalson A, Franken EA, Smith W. Cost-effectiveness and safety of selective use of low-osmolality contrast media. *Acad Radiol*. 1994;1:59-62.
31. Caro JJ, Trindade E, McGregor M. The cost-effectiveness of replacing high-osmolality with low-osmolality contrast media. *AJR Am J Roentgenol*. 1992;159:869-874.
32. Steinberg EP, Moore RD, Powe NR, Gopalan R, Davidoff AJ, Litt M, et al. Safety and cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. *N Engl J Med*. 1992;326:425-430.

33. Tippins RB, Torres WE, Baumgartner BR, Baumgarten DA. Are screening serum creatinine levels necessary prior to outpatient CT examinations? *Radiology*. 2000;216:481-484.
34. Choyke PL, Cady J, DePollar SL, Austin H. Determination of serum creatinine prior to iodinated contrast media: is it necessary in all patients? *Tech Urol*. 1998;4:65-69.