Update: Prevention of Contrast-Induced Nephropathy in the Emergency Department

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Study objective: Some studies have suggested that there exist therapies that can prevent contrast-induced nephropathy, which are practical in an emergency setting. This evidence-based emergency medicine (EBEM) critical appraisal reviews the literature, including additional studies appearing since the publication of an earlier EBEM review in 2007.

Methods: The updated search for randomized controlled trials from 2006 to 2008 complemented the previous search from 1966 to 2005. The methodological quality of the studies was assessed. Qualitative methods were used to summarize the study results.

Results: The search identified 2 studies not included in the previously published review of prophylactic therapies against contrast-induced nephropathy, yielding a total of 4 blinded, randomized, placebo-controlled trials involving bicarbonate and ascorbic acid. The present study of bicarbonate found a similar benefit as the previously reviewed bicarbonate trial. The early termination of both bicarbonate studies presents significant analytical concerns. The present study of ascorbic acid failed to reproduce the prophylactic effect of ascorbic acid observed in the previously reviewed trial. This difference in outcomes of the 2 ascorbic acid trials is related to variations in the volume of contrast and procedural hydration between the studies.

Conclusion: Although bicarbonate should still be considered a low-risk prophylactic agent, it appears that other factors (type of contrast agent, volume of contrast, and procedural hydration protocol) have an important influence on the risk of contrast-induced nephropathy. For the emergency physician, limiting exposure to contrast agents and adequate precontrast hydration are still the first line of defense against contrast-induced nephropathy. [Ann Emerg Med. 2009;54:e1-e5.]

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In 2007, we published an evidence-based emergency medicine (EBEM) review of therapies to prevent contrast-induced nephropathy, which were practical in an emergency setting.[1] We performed an updated review on this topic using the same search strategies and selection criteria described in our previous review.[1] We searched MEDLINE, using the PubMed interface, between January 2006 and April 2008 and EMBASE from January 2006 to April 2008 with the Ovid Technologies interface and identified 2 eligible randomized controlled trials by Masuda et al[2] and Boscheri et al[3] that were not included in our original review. We also screened the bibliographies of the 2 articles and did not find any additional relevant studies. We also searched relevant databases within the Cochrane Library, particularly the Central Register of Controlled Trials, for new studies and protocols through April 2008 and found 0 articles.

The studies added in this update by Masuda et al[2] investigated prophylactic administration of bicarbonate, whereas Boscheri et al[3] tested ascorbic acid. For comparison, we included studies from our previous review by Merten et al[4] and Spargias et al,[5] who also investigated bicarbonate and vitamin C, respectively. According to Masuda et al,[2] the impetus to restudy the Merten et al[4] bicarbonate prophylaxis protocol was to narrow the inclusion criteria to patients undergoing emergency cardiac catheterizations. Boscheri et al[3] tested ascorbic acid with better control over the volume of contrast media in the intervention and comparison groups.

From Table 1, we can see a comparison of the characteristics across the 4 studies. Important differences between the studies can be seen in the areas of inclusion criteria, contrast agents (type and volume), and procedural hydration. The Masuda et al[2] study was the only one to narrow the inclusion criteria to only those patients undergoing emergency cardiac catheterizations, whereas the other studies included emergency and nonemergency cases. Both bicarbonate studies used a nonionic low-osmolality contrast medium, whereas Spargias et al[5] allowed a mixture of contrast agents and Boscheri et al[3] only used a nonionic iso-osmolar agent. The volume of contrast agents administered in the study by Spargias et al[5] was almost twice that of the other studies (≈280 mL versus <140 mL). The Boscheri et al[3] study used the largest volume (250 mL/hour

Table 1. Summary of the 4 studies to prevent contrast-induced nephropathy, including 2 appraised in a previous review.

Study Characteristics	Merten et al,[4] 2004 (n=119), Bicarbonate	Masuda et al,[2] 2007 (n=59), Bicarbonate	Spargias et al,[5] 2004 (n= 231), Ascorbic Acid	Boscheri et al,[3] 2007 (n=143), Ascorbic Acid
Population	Avg.* age = 67.9 years Avg.* Cr = 1.80 mg/dL Procedures: Emergency and nonemergency cardiac catheterizations, CTs and other procedures (brachytherapy, renal and peripheral arteriograms, aortograms, embolization) Exclusion criteria: Severe or recent ESRD, uncontrolled HTN, pregnancy, or recent use of dopamine, mannitol or fenoldopam Contrast agent: 100% nonionic low osmolality IV fluid volume: Intervention: 135±76 mL Comparison: 133±62 mL	Avg.* age = 75.5 years Avg.* Cr = 1.32 mg/dL Procedures: Only emergency cardiac catheterizations Exclusion criteria: Severe or recent ESRD, pregnancy, or recent exposure to radiographic contrast media mannitol, fenoldopam, NAC or nonstudy sodium bicarbonate Contrast agent: 100% nonionic, low osmolality IV fluid volume: Intervention: 112±89 mL Comparison: 120±61 mL	Avg.* age = 65.5 years Avg.* Cr = 1.45 mg/dL Procedures: Emergency and nonemergency cardiac catheterizations Exclusion criteria: Severe or recent ESRD. Contrast agent: 59% Nonionic iso-osmolar 37% Low osmolar/nonionic 4% Low osmolar/ionic IV fluid volume: Intervention: 287±148 mL Comparison: 261±128 mL	Avg.* age = 71.0 years Avg.* Cr = 1.74 mg/dL Procedures: Emergency and nonemergency cardiac catheterizations Exclusion criteria: Severe or recent ESRD, pregnancy, or recent exposure to NAC or radiographic contrast media, MI <3 months, cardiogenic shock, vasopressors, ejection fraction <25% Contrast agent: 100% nonionic iso-osmolar IV fluid volume: Intervention: 99±46 mL Comparison: 112±67 mL
Intervention	$NaHCO_3$ 154 mEq/L $NaHCO_3$in D5W 1000 mL at 3 mL/kg per hour for 1 hour precontrast and 1 mL/kg per hour during the contrast exposure and 6 hours postcontrast	$NaHCO_3$ 154 mEq/L $NaHCO_3$in D5W 1000 mL at 3 mL/kg per hour for 1 hour precontrast and 1 mL/kg per hour during the contrast exposure and 6 hours postcontrast	Ascorbic acid 3 g oral, 2 hours precontrast, and 2 g the night of and the morning after the procedure. NS at 50–125 mL/hour starting at least 2 hours precontrast and continued for 6 hours.	Ascorbic acid 1g 20 minutes before dye and NS 500 mL 2 hours before, and NS 500 mL during/after over 6 hours
Comparison	Hydration: 154 mEq/L of NaCl in 5% D5W 3 mL/kg per hour for 1 hour precontrast and 1 mL/kg per hour during the contrast exposure and 6 hours postcontrast	Hydration—NS 3 mL/kg per hour for 1 hour precontrast and 1 mL/kg per hour during the contrast exposure and 6 hours postcontrast	Hydration: NS at 50–125 mL/hour starting at least 2 hours precontrast and continued for 6 hours.	Hydration—NS 500 mL 2 hours before, and NS 500 mL during/after over 6 hours
Outcome measures	CIN: increase in serum creatinine level of 0.5 mg/dL or an increase in serum creatinine level by 25% at 48 hours postcontrast	CIN: increase in serum creatinine level of 0.5 mg/dL or an increase in serum level creatinine by 25% at 48 hours postcontrast	CIN: increase in serum creatinine level of 0.5 mg/dL or an increase in serum creatinine level by 25% at 48 hours postcontrast	CIN: increase in serum creatinine level by 25% at 48 hours postcontrast

CT, Computed tomography; *ESRD*, end stage renal disease; *HTN*, hypertension; *NAC*, N-acetylcysteine; *MI*, myocardial infarction; *$NaHCO_3$*, sodium bicarbonate; *NS*, normal saline solution; *CIN*, contrast-induced nephropathy; *NaCl*, sodium chloride.
*Weighted average.

Table 2. Susceptibility to bias of the 4 studies to prevent contrast-induced nephropathy, including 2 appraised in a previous review.

Potential Bias	Merten et al,[4] 2004, Bicarbonate	Masuda et al,[2] 2007, Bicarbonate	Spargias et al,[5] 2004, Ascorbic Acid	Boscheri et al[3] 2007, Ascorbic Acid
Randomization	Single-center randomization assigned by the pharmacy according to a computer-generated schedule	Computer-generated random numbers determined randomization	Single center Randomization was in blocks of 10	Single-center randomization technique not mentioned
Concealment	Adequate	Adequate	Adequate	Adequate
Blinding	Treatment assignment blinded to patients, providers and assessors	No blinding	Double blinded, but the identities of those who were blinded not specified	Double blinded to patients and investigators
Intention to treat	Yes	Two patients (1 for each group) were excluded after randomization	Yes	Yes
Baseline comparisons	Well balanced for risk factors for CIN	Well balanced for risk factors for CIN	Well balanced for risk factors for CIN	Well balanced for risk factors for CIN
Cointerventions	Same hydration protocols in both intervention and comparison groups	Same hydration protocols in both intervention and comparison groups	Similar hydration protocols in both intervention and comparison groups	Similar hydration protocols in both intervention and comparison groups
Completeness of follow-up	7% patients lost to follow-up were excluded from analysis. No change in the primary result when patients lost to follow-up were added back into the analysis	All patients accounted for except for 1 patient in each group who was excluded after being randomized	3% patients lost to follow-up were excluded from analysis. No change in the primary result when patients lost to follow-up were added back into the analysis	All patients accounted for

Boscheri et al[3] versus 125 mL/hour Spargias et al[5] versus 3mL/kg Merten et al[4] and Masuda et al[2]) of pre- and postprocedural hydration compared with the other studies.

Table 2 compares the potential sources of bias between the studies under review. Concealment and blinding were not evident in the study by Masuda et al.[2] Intention-to-treat analysis was also not performed in the studies by Masuda et al[2] and Boscheri et al.[3] Merten et al[4] and Spargias et al[5] lost 3% and 7% of their patients to follow-up, respectively. Merten et al[4] accounted for their patients lost to follow-up by including their baseline data into the analysis as the last observation carried forward. They found that reanalyzing their data this way was not informative and did not affect their results. Spargias et al[5] conducted a sensitivity analysis of patients lost to follow-up by assuming their changes in postprocedural renal function reflected the change observed in the overall study population No significant differences in their results were noted in this sensitivity analysis. What is not covered as a potential source of bias in Table 2 is the effect of early termination of both bicarbonate studies. Merten et al[4] estimated a total sample size of 260 patients required to adequately power (80%; $\alpha=0.05$) the study to detect a change in the incidence of contrast-induced nephropathy from 15% to 5%. Masuda et al,[4] using similar calculations (14% to 2%), estimated a sufficient sample size of 160 patients. Both the Merten et al[4] (n=137; 18 excluded after randomization) and the Masuda et al[2] (n=61; 2 excluded after randomization) trials were terminated early because an interim analysis determined that the evidence in favor of the intervention made it unethical to continue to recruit patients into the comparison arms. This may have led to an overestimation of the treatment effect. This bias arises because random fluctuations toward greater and lesser treatment effects occur naturally in randomized clinical trials, if the decision to interrupt the trial and analyze the data occurred during a "random high," the resulting estimate of the treatment effect maybe misleading.[6,7]

Table 3 compares the results of the studies. There is significant heterogeneity of the event rates in the comparison groups across the studies. The Masuda et al[2] comparison group had a significantly higher incidence of contrast-induced nephropathy (34.5%) than did the comparable groups within the other studies (20.4%,[5] 13.6%,[4] and 4.3%,[3] respectively). We believe the likely explanation for the higher incidence of contrast-induced nephropathy in the Masuda et al[2] study is multifactorial. The Masuda et al[2] patients were most likely sicker because only emergency cardiac catheterization cases were included, whereas the other studies included both emergency and nonemergency patients. Masuda et al[2] used a nonionic low-osmolar contrast agent with a higher risk of kidney injury compared to the iso-osmolar medium used in the ascorbic acid studies.[8] Finally, the bicarbonate compared to the vitamin C studies had significantly smaller-volume pre- and postprocedural hydration protocols. Furthermore, only two thirds of the patients in the Masuda et al[2] study received the full amount of

Table 3. Results of the 4 studies to prevent contrast-induced nephropathy, including 2 appraised in a previous review.

Outcomes		Merten et al,[4] 2004, Bicarbonate		Masuda et al,[2] 2007, Bicarbonate		Spargias et al,[5] 2004, Ascorbic Acid		Boscheri et al,[3] 2007, Ascorbic Acid	
Risk for CIN	Treatment	1/60	1.7%	2/30	6.7%	11/118	9.3%	5/74	6.8%
	Comparison	8/59	13.6%	10/29	34.5%	23/113	20.4%	3/69	4.4%
Relative risk of CIN (95% CI)		0.12 (0.02–0.72)		0.19 (0.05–0.81)		0.46 (0.24–0.88)		1.55 (0.3–6.3)	
Number needed to treat (95% CI)		8.4 (6.8–40)		4 (2.1–12.0)		9.1 (5.4–52.7)		NA	

NA, Not applicable (because the effect was not statistically significant; RR includes 1.0.)

fluid before the procedure because some patients were sent to catheterization before the full hour.

In contrast, the comparison group in the study by Boscheri et al[3] had the lowest incidence of contrast-induced nephropathy (4.3%) observed. These patients received the smallest volume of only a nonionic iso-osmolar contrast agent and were given the largest volume of pre- and postprocedural hydration.

Table 3 also compares the effectiveness of the interventions in preventing contrast-induced nephropathy. The 2 studies using bicarbonate compared to the trial of ascorbic acid by Spargias et al[5] had the greatest reduction in relative risk (88% and 81% versus 54%) of kidney injury. Not surprisingly, the study by Boscheri et al,[3] with the lowest incidence of kidney injury in their comparison group, failed to show a benefit to their intervention (ascorbic acid). The large confidence intervals observed by Boscheri et al[3] reflect the study's relatively small sample and effect sizes.

In conclusion, from this updated review the most effective intervention appears to be bicarbonate, although both these studies have significant limitations related to bias from the low volumes of pre- and postprocedural hydration and early study termination. What is clear from these trials is that factors other than their primary interventions (bicarbonate or ascorbic acid) had an important effect on the risk of contrast-induced nephropathy. Independent risk factors for contrast-induced nephropathy include the type of contrast agent (low versus iso-osmolar), volume of contrast (>140 mL),[9] and procedural hydration protocols.[10,11] For the emergency physician faced with the decision to expose a patient with renal insufficiency to intravenous contrast media, bicarbonate may represent a relatively low-risk prophylactic agent. However, withholding or limiting the volume of intravenous contrast, selecting a less nephrotoxic contrast agent, and appropriate levels of hydration should also be considered.[12,13]

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REFERENCES

1. Sinert R, Doty CI. Prevention of contrast-induced nephropathy in the emergency department. *Ann Emerg Med.* 2007;50:335-345.
2. Masuda M, Yamada T, Mine T, et al. Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure. *Am J Cardiol.* 2007;100:781-786.
3. Boscheri A, Weinbrenner C, Botzek B, et al. Failure of ascorbic acid to prevent contrast-media induced nephropathy in patients with renal dysfunction. *Clin Nephrol.* 2007;68:279-286.
4. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA.* 2004;291:2328-2334.
5. Spargias K, Alexopoulos E, Kyrzopoulos S, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation.* 2004;110:2837-2842.
6. Bassler D, Ferreira-Gonzalez I, Briel M, et al. Systematic reviewers neglect bias that results from trials stopped early for benefit. *J Clin Epidemiol.* 2007;60:869-873.
7. Heffner AC, Milbrandt EB, Venkataraman R. Trials stopped early for benefit? Not so fast! *Crit Care.* 2007;11:305.
8. McCullough PA, Bertrand ME, Brinker JA, et al. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol.* 2006;48:692-699.
9. Freeman RV, O'Donnell M, Share D, et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol.* 2002;90:1068-1073.
10. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med.* 2002;162:329-336.
11. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract.* 2003;93:C29-34.
12. Stacul F, Adam A, Becker CR, et al. Strategies to reduce the risk of contrast-induced nephropathy. *Am J Cardiol.* 2006;98(Suppl): 59K-77K.
13. Solomon R, Deray G. How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations. *Kidney Int Suppl.* 2006;(100):S51-53.

Critically Appraised Topic (CAT): What interventions are available to prevent the renal failure and death associated with contrast-induced nephropathy? 2008 Update.

Question

In patients with baseline renal insufficiency, which interventions are effective in preventing contrast-induced nephropathy and its complications, given the resource and time constraints in a busy emergency department (ED)?

Reviewed by

Sinert RH, Doty C

Date of search

May 2008

Expiration date

April 2010

Clinical bottom line

Evidence from randomized trials shows that the intervention (bicarbonate) under review is appropriate to an ED setting and decreased the risk of contrast-induced nephropathy. The case for the effectiveness of ascorbic acid was less certain. Independent risk factors for contrast-induced nephropathy include the type of contrast agent (low versus iso-osmolar), volume of contrast (>140 mL), and procedural hydration protocols

Search strategy

MEDLINE, EMBASE, the Cochrane Library from the dates of origin through April 2008.

Citations

Primary: 2 fully reported additional randomized trials

(Updated review) Masuda M, Yamada T, Mine T, et al. Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergency coronary procedure. *Am J Cardiol.* 2007;100:781-786.

(Updated review) Boscheri A, Weinbrenner C, Botzek B, et al. Failure of ascorbic acid to prevent contrast-media induced nephropathy in patients with renal dysfunction. *Clin Nephrol*. 2007;68:279-286.

(Previous review) Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA.* 2004;291:2328-2334.

(Previous review) Spargias K, Alexopoulos E, Kyrzopoulos S, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation.* 2004;110:2837-2842.

Primary study characteristics

Study Population

Patients with baseline renal insufficiency over age 18 years receiving radiocontrast agents.

Interventions

Bicarbonate: 1 New study
Ascorbic acid: 1 New study

Outcome Measures

Contrast-induced nephropathy was defined by either a proportional increase of 25% in serum creatinine level or an absolute increase in serum creatinine level by 0.5 mg/dL from baseline 48 hours after contrast exposure. In addition, we reviewed each trial for changes in the rates of renal failure requiring inhospital dialysis and death between intervention and control groups.

Critical appraisal

Fair to good quality was observed in all trials.

Results

Intervention	# Studies	Relative Risk of Contrast-Induced Nephropathy Intervention vs Comparison (95% CI)
Bicarbonate (updated review)	1	0.19 (0.05–0.81)
Bicarbonate (previous review)	1	0.12 (0.02–0.72)
Ascorbic acid (updated review)	1	1.55 (0.3–6.3)
Ascorbic acid (previous review)	1	0.46 (0.24–0.88)

No study was sufficiently powered to detect significant improvements in mortality rate or the rate of renal failure requiring dialysis with their interventions.