Sodium Bicarbonate Therapy for Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis

Sankar D. Navaneethan, MD, MPH, Sonal Singh, MD, MPH, Suresh Appasamy, MD, Richard E. Wing, MD, and Ashwini R. Sehgal, MD

Background: Optimal hydration measures to prevent contrast-induced nephropathy are controversial.

Study Design: We conducted a systematic review and meta-analysis using the MEDLINE database (1966 to January 2008), EMBASE (January 2008), and abstracts from conference proceedings.

Setting & Population: Adult patients undergoing contrast procedures.

Selection Criteria for Studies: Randomized controlled trials comparing intravenous hydration with sodium bicarbonate with hydration with intravenous normal saline for prevention of contrast-induced nephropathy.

Intervention: Hydration with intravenous sodium bicarbonate with or without N-acetylcysteine versus hydration with normal saline with or without N-acetylcysteine.

Outcomes: Contrast-induced nephropathy, need for renal replacement therapy, and worsening of heart failure.

Results: Twelve trials (1,854 participants) were included. Sodium bicarbonate significantly decreased the risk of contrast-induced nephropathy (12 trials, 1,652 patients; odds ratio [OR], 0.46; 95% confidence interval [CI], 0.26 to 0.82; I² = 55.9%) without a significant difference in need for renal replacement therapy (9 trials, 1,215 patients; OR, 0.50; 95% CI, 0.16 to 1.53; I² = 0%), in-hospital mortality (11 trials, 1,840 patients; OR, 0.51; 95% CI, 0.15 to 1.69), or congestive heart failure compared with controls. Similar results were seen for the risk of contrast-induced nephropathy when sodium bicarbonate was compared with normal saline alone (OR, 0.39; 95% CI, 0.20 to 0.77), but not when sodium bicarbonate/N-acetylcysteine combination was compared with N-acetylcysteine/normal saline combination (OR, 0.68; 95% CI, 0.34 to 1.37). A subgroup analysis limited to published trials showed similar results (OR, 0.26; 95% CI, 0.10 to 0.64; I² = 63.3%), whereas unpublished studies showed a nonsignificant decrease (OR, 0.85; 95% CI, 0.46 to 1.57; I² = 25.9%) in risk of contrast-induced nephropathy.

Limitation: Publication bias and heterogeneity.

Conclusion: Hydration with sodium bicarbonate decreases the incidence of contrast-induced nephropathy in comparison to hydration with normal saline without a significant difference in need for renal replacement therapy and in-hospital mortality. Larger studies analyzing patient-centered outcomes are needed.

INDEX WORDS: Hydration; sodium bicarbonate; contrast-induced nephropathy; acute renal failure.

The incidence of contrast-induced nephropathy is increasing in the United States and across the globe as a result of increasing use of diagnostic procedures. Contrast-induced nephropathy is the third most common cause of hospital-acquired kidney failure.1 Although only a small percentage of patients who undergo coronary angiography require dialysis within 1 month of contrast administration,2 contrast-induced nephropathy is associated with lengthened hospital stays, increased cost, and increased risk of death.3-6

Combination regimens including the use of N-acetylcysteine, hydration with normal saline or sodium bicarbonate, and use of low-osmolar contrast medium have been proposed to prevent the development of contrast-induced nephropathy.7-9 The role of N-acetylcysteine in the prevention of contrast-induced nephropathy is unclear. Fifteen randomized controlled trials and their
meta-analyses have shown inconsistent results on the efficacy of N-acetylcysteine for the prevention of contrast-induced nephropathy because some trials claim that N-acetylcysteine is effective in the prevention of contrast-induced nephropathy, whereas others have argued for more definitive evidence of benefit10-12 before it can be widely recommended. In 2006, a consensus panel for contrast-induced nephropathy recommended volume supplementation with either normal saline or sodium bicarbonate for the prevention of contrast-induced nephropathy.13 It is unclear whether one approach to hydration is superior to the other in preventing contrast-induced nephropathy.

Several clinical trials that analyzed the role of sodium bicarbonate in the prevention of contrast-induced nephropathy have been published recently.14-16 However, there has been no large-scale confirmation to date of the benefits seen in early trials.14 There is a lack of a robust analysis that explores the additive effect of N-acetylcysteine and bicarbonate prophylaxis. The benefit-risk profile of sodium bicarbonate has not been systematically evaluated in the literature.

Our primary objective is to systematically review the evidence of benefits of hydration with sodium bicarbonate compared with hydration with normal saline in the prevention of contrast-induced nephropathy. As secondary objectives, we also assessed differences in the need for renal replacement therapy, in-hospital mortality, length of hospital stay, and risk of worsening heart failure with the use of sodium bicarbonate in these trials.

**METHODS**

**Data Sources and Search Strategy**

We searched MEDLINE (1966 to January 2008), EMBASE (January 2008), and abstracts presented in 2004 to 2007 at the American Society of Nephrology, National Kidney Foundation, European Renal Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, American Heart Association, and Radiology Society of America annual meetings by using the medical subject heading terms contrast nephropathy, sodium bicarbonate, hydration, and randomized trial for relevant trials. References of the included studies were searched for additional studies. There were no language restrictions. Two reviewers (S.D.N. and S.A.) independently and in duplicate screened all abstracts that indicated the study was a randomized controlled trial evaluating sodium bicarbonate in the prevention of contrast-induced nephropathy. After obtaining the candidate trials, the same reviewers independently and in duplicate assessed eligibility from the full-text articles.

**Study Selection and Outcome Measures**

Eligible studies had the following characteristics: (1) they were randomized control trials of any duration for prevention of contrast-induced nephropathy, (2) the intervention was hydration with sodium bicarbonate versus hydration with normal saline with or without the addition of N-acetylcysteine as long as the only difference in the 2 arms was the use of sodium bicarbonate, (3) trial participants (with or without preexisting kidney disease) underwent any contrast procedure that was either elective or emergent, and (4) the studies reported the incidence of the outcome of interest, i.e., contrast-induced nephropathy (including zero events) in both arms.

The primary outcome measure was the development of contrast-induced nephropathy, defined as either a greater than 25% or a greater than 0.5-mg/dL increase in serum creatinine level from baseline within 96 hours after contrast administration. Secondary outcome measures included: (1) the need for renal replacement therapy, (2) in-hospital mortality, (3) length of hospital stay, (4) worsening of preexisting congestive heart failure or the development of acute pulmonary edema, and (5) change in serum bicarbonate levels at the end of the study period.

**Data Collection**

Two reviewers (S.D.N. and S.A.) extracted data after assessing and reaching consensus for eligible studies by using a standardized data extraction form. Any discrepancies between the 2 reviewers were resolved by discussion with an arbitrator (S.S.). The same reviewers independently assessed each trial and extracted data about the characteristics of participants, study setting (emergency versus elective), protocol for the infusion of bicarbonate or normal saline and N-acetylcysteine, baseline kidney function, type of contrast used, and outcomes measured. We contacted investigators when specific aspects of the data regarding primary and secondary outcome measures (need for renal replacement therapy and congestive heart failure) required clarification. The quality of included studies was assessed by 2 reviewers (S.D.N. and S.A.) without blinding to authorship or journal. The quality items were assessed by using the validated Jadad score (randomization, blinding and withdrawals, and drop outs).17

**Data Analysis and Synthesis**

Dichotomous data (contrast-induced nephropathy, need for renal replacement therapy, in-hospital mortality, and worsening of heart failure) were analyzed using the odds ratio (OR) measure and its 95% confidence interval (CI), and continuous variables (change in serum bicarbonate level at the end of the study period) were analyzed using the weighted mean difference and its 95% CI. All P values are reported as 2 sided. Risks estimated from individual trials were pooled using the DerSimonian-Laird random-effects model.18 In measures of relative risk and ORs, if both arms had zero cells, they could not be included in the meta-analysis. However, if 1 arm had zero cells, a continuity correction of
Heterogeneity across the included studies was analyzed using heterogeneity \( I^2 \) (Cochrane Q) statistic and \( \chi^2 \) test. \( I^2 \) values greater than 25%, 50%, and 75% were considered evidence of low, moderate, and severe statistical heterogeneity, respectively.\(^{19}\) If substantial statistical heterogeneity were noted (\( I^2 \) > 50%), we planned to explore individual study characteristics and those of subgroups of the main body of evidence.

We performed sensitivity analyses to explore the influence of statistical models (fixed- and random-effects model) on effect size and the influence of each study by excluding 1 study at a time) to assess the robustness of results. We conducted prespecified sensitivity (subgroup) analyses based on the severity of kidney disease in participants at baseline (defined as studies that recruited participants with estimated glomerular filtration rate <60 mL/min/1.73 m\(^2\) versus those with estimated glomerular filtration rate >60 mL/min/1.73 m\(^2\)), setting (emergency versus elective contrast procedure), and publication status (journal published versus abstracts). All analyses were undertaken in RevMan 4.2.10.

**RESULTS**

**Search Results**

The combined search of MEDLINE, EMBASE, and the conference proceedings identified 323 articles, of which 270 were excluded because they were either nonrandomized studies or evaluated interventions or outcomes irrelevant to this review. Full-text assessment of 53 potentially relevant articles resulted in identification of 12 eligible trials (6 published trials and 6 abstracts from conference proceedings) involving 1,854 participants.\(^{14-16,20-28}\) Trials excluded at this stage were either review articles or studies that analyzed other outcomes (Fig 1).

**Trial Characteristics**

Five of the 12 studies compared sodium bicarbonate plus \( N \)-acetylcysteine with sodium chloride plus \( N \)-acetylcysteine,\(^ {20,21,23,25,27}\) whereas 4 other studies compared sodium bicarbonate with normal saline alone.\(^ {14-16,24}\) Three studies compared sodium bicarbonate plus \( N \)-acetylcysteine with sodium chloride plus \( N \)-acetylcysteine, as well as sodium bicarbonate alone with normal saline alone.\(^ {22,26,28}\) The number of participants in these studies ranged from 27 to 353. Six studies enrolled patients undergoing elective contrast procedures,\(^ {14,16,21,22,25,26}\) and 2 studies enrolled patients undergoing emergency contrast procedures.\(^ {15,20}\) In 4 studies, we could not assess whether participants underwent elective or emergent procedures, and for this analysis, we considered this a separate group that had participants undergoing both elective and emergency contrast procedures. Most studies included participants who underwent coronary angiography procedures and enrolled participants with underlying decreased kidney function, although this was variable. All studies used nonionic contrast with either iso-osmolarity or low osmolarity (Table 1).\(^ {14-16,20-28}\)

The treatment regimen varied among studies and between the 2 comparisons. Seven trials used 154 mEq/L of sodium bicarbonate at 3 mL/kg/h for 1 hour before contrast, then 1 mL/kg/h for 6 hours after contrast,\(^ {14,15,21,23,25,27}\) whereas Ozcan et al\(^ {16}\) used 1 mL/kg/h 6 hours before and after contrast. Recio-Mayoral et al\(^ {20}\) used 5 mL/kg/h of sodium bicarbonate solution for 1 hour before and then 1.5 mL/kg/h for 12 hours after contrast, and Kim et al\(^ {22}\) used 80 mEq/L at 1 mL/kg/h 12 hours before and after contrast. The sodium chloride arm of the included studies also had different protocols, with 154 mEq/L of sodium chloride at 3 mL/kg/h for 1 hour before contrast and then 1 mL/kg/h for 6 hours after contrast as the widely used protocol. Other characteristics of participants and interventions of the included trials are listed in Table 1. Overall, the
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Baseline Kidney Function</th>
<th>Intervention (n)</th>
<th>Contrast Material</th>
<th>Definition of CIN</th>
<th>End Point Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merten et al, 14 2004</td>
<td>Elective cardiac and noncardiac procedures</td>
<td>Cr ≥ 1.1 and &lt; 8.0 mg/dL</td>
<td>0.9% NaCl (59) v NaHCO₃ (60)</td>
<td>Iopamidol</td>
<td>≥25% ↑ Cr in 2 d</td>
<td>CIN, change in Cr and Cr clearance, need for RRT, urinary pH</td>
</tr>
<tr>
<td>Masuda et al, 15* 2007</td>
<td>Emergency diagnostic or interventional coronary angiography</td>
<td>Cr ≥ 1.1 mg/dL (or) CG GFR &lt; 60 mL/min</td>
<td>0.9% NaCl (29) v NaHCO₃ (30)</td>
<td>Iopamidol</td>
<td>&gt;25% ↑ Cr or &gt; 0.5 mg/dL ↑ Cr in 2 d</td>
<td>CIN, change in Cr, eGFR, urinary pH, blood HCO₃ level, need for RRT, death, heart failure</td>
</tr>
<tr>
<td>Ozcan et al, 16 2007</td>
<td>Elective coronary angiography or PCI</td>
<td>Cr ≥ 1.2 and &lt; 4.0 mg/dL</td>
<td>0.9% NaCl (88) v NaCl + NAC (88) v NaHCO₃ (88)</td>
<td>Iopamidol</td>
<td>≥25% ↑ Cr or ≥ 0.5 mg/dL ↑ Cr in 48 h</td>
<td>CIN, SUN, Cr clearance</td>
</tr>
<tr>
<td>Recio-Mayoral et al, 20 2007</td>
<td>Emergency coronary angiography or PCI</td>
<td>Cr 0.2-1.2 mg/dL</td>
<td>0.9% NaCl + NAC (55) v NaHCO₃ + NAC (56)</td>
<td>Ioxaglate</td>
<td>≥0.5 mg/dL ↑ Cr or ≥ 25% ↑ Cr in 3 d</td>
<td>CIN, need for RRT, death, development of pulmonary edema</td>
</tr>
<tr>
<td>Briguori et al, 21† 2007</td>
<td>Elective coronary and peripheral vascular procedures</td>
<td>Cr ≥ 2.0 and ≤ 8.0 mg/dL (or) eGFR &lt; 40 mL/min/1.73 m²</td>
<td>0.9% NaCl + NAC (111) v NaHCO₃ + NAC (108) v 0.9% NaCl + NAC + vitamin C (107)</td>
<td>Iodixanol</td>
<td>≥25% ↑ Cr or ≥ 0.5 mg/dL ↑ Cr in 48 h in GFR in 48 h or need for dialysis</td>
<td>CIN, change in GFR, need for RRT, death, urine pH, change in SUN</td>
</tr>
<tr>
<td>Kim et al, 22 2007</td>
<td>Elective coronary angiography</td>
<td>Cr ≤ 1.5 mg/dL (or) proteinuria ≥ 500 mg/dl</td>
<td>0.9% NaCl (24) v 0.9% NaCl + NAC (20) v NaHCO₃ (25) v NaHCO₃ + NAC (31)</td>
<td>Iodixanol</td>
<td>≥25% ↑ Cr in 2 d</td>
<td>CIN, RRT</td>
</tr>
<tr>
<td>Lin et al, 23 2007</td>
<td>Diagnostic or interventional procedure</td>
<td>Cr ≤ 2.0 mg/dL</td>
<td>0.9% NaCl + NAC (24) v NaHCO₃ + NAC (21)</td>
<td>Iopamidol</td>
<td>≥25% ↑ Cr in 3 d</td>
<td>CIN, RRT</td>
</tr>
<tr>
<td>Chen et al, 24 2007</td>
<td>Coronary or renal arteriography</td>
<td>CG eGFR &lt; 60 mL/min/1.73 m²</td>
<td>0.9% NaCl (50) v NaHCO₃ (55)</td>
<td>Iohexol</td>
<td>&gt;25% ↑ Cr or ≥ 0.5 mg/dL ↑ Cr in 72 h</td>
<td>CIN, RRT</td>
</tr>
<tr>
<td>Heguilen et al, 25 2007</td>
<td>Elective angiographic study or intervention</td>
<td>Cr ≥ 1.25 mg/dL (or) CG eGFR &lt; 50 mL/min/1.73 m²</td>
<td>0.9% NaCl + NAC (9) v NaHCO₃ (9) v NaHCO₃ + NAC (9)</td>
<td>Ioversol</td>
<td>≥25% ↑ Cr in 2-3 d</td>
<td>CIN, RRT</td>
</tr>
<tr>
<td>Shaikh et al, 26† 2007</td>
<td>Elective angiographic study or intervention</td>
<td>Cr ≥ 1.6 mg/dL in nondiabetics and &gt; 1.4 mg/dL in diabetic patients or eGFR &lt; 50 mL/min/1.73 m²</td>
<td>0.9% NaCl (80) v NaHCO₃ (79) &amp; 0.9% NaCl + NAC (81) v NaHCO₃ + NAC (80)</td>
<td>NA</td>
<td>≥25% ↑ Cr or ≥ 0.5 mg/dL ↑ Cr in 48 h</td>
<td>CIN</td>
</tr>
</tbody>
</table>

(Continued)
quality of included trials was low to moderate, and we did not have sufficient data to discern differences in results based on trial quality (Table 2).

**Study Outcomes**

**Contrast-Induced Nephropathy**

Sodium bicarbonate–based hydration regimens significantly decreased the risk of contrast-induced nephropathy compared with control regimens (12 trials, 1,652 patients; \( n \) = 75 of 829 versus 128 of 823; OR, 0.46; 95% CI, 0.26 to 0.82; \( P = 0.008 \)).14-16,20-28 There was moderate statistical heterogeneity noted among the included trials (heterogeneity \( I^2 = 24.95 \%; \ P = 0.009 \); Fig 2). Similar results favoring regimens using sodium bicarbonate were seen in trials comparing sodium bicarbonate alone versus normal saline alone (7 trials, 839 patients; OR, 0.39; 95% CI, 0.20 to 0.77; \( P = 0.006 \)), but not when sodium bicarbonate/N-acetylcysteine combination was compared with N-acetylcysteine/normal saline combination (8 trials, 813 patients; OR, 0.68; 95% CI, 0.34 to 1.37; \( P = 0.3 \)) in a subgroup analysis.

**Need for Renal Replacement Therapy**

There was no difference in the need for renal replacement therapy with sodium bicarbonate compared with controls (9 trials, 1,215 patients; \( n \) = 5 of 612 versus 10 of 603; OR, 0.50, 95% CI, 0.16 to 1.53; \( P = 0.2 \)).14-16,20-23,25,28 There was no statistical heterogeneity noted among the included trials (heterogeneity \( I^2 = 1.65 \%; \ P = 0.9 \); Fig 3).

**In-Hospital Mortality**

There was no difference in in-hospital mortality with sodium bicarbonate compared with controls (11 trials, 1,640 patients; 4 of 826 versus 9 of 814; OR, 0.51; 95% CI 0.15 to 1.69; \( P = 0.3 \)). There was no statistical heterogeneity among the included trials (heterogeneity \( I^2 = 1.65 \%; \ P = 0.4 \)).

**Congestive Heart Failure/Pulmonary Edema**

Seven studies reported no worsening of congestive heart failure or development of acute pulmonary edema in patients included in the study. In 2 studies (\( n = 170 \)), there was no difference noted in the worsening of congestive heart failure with sodium bicarbonate in comparison to normal saline (OR, 0.85; 95% CI, 0.32 to 2.24; \( P = 0.7 \)).18,20 Relevant data were not available in 3 studies.

### Table 1 (Cont’d). Characteristics of Patients, Interventions, and Outcomes of Included Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Intervention (n)</th>
<th>Baseline Kidney Function</th>
<th>Contrast Material</th>
<th>Definition of CIN</th>
<th>End Point Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saidin et al,27</td>
<td>2006</td>
<td>Coronary angiography or angioplasty</td>
<td>0.9% NaCl + NAC (27) v NaHCO(_3) + NAC (28)</td>
<td>NA</td>
<td>GFR &lt; 60 mL/min/1.73 m(^2)</td>
<td>CIN, RRT, 30-d, 6 mo, all cause mortality, GFR at 2-8 wk postprocedure</td>
</tr>
<tr>
<td>Bar et al,28</td>
<td>2008</td>
<td>Coronary angiography</td>
<td>0.9% NaCl (87) v NaHCO(_3) (85) &amp; 0.9% NaCl/NAC (78) v NaHCO(_3) (73)</td>
<td>GFR &gt; 60 mL/min/1.73 m(^2)</td>
<td>Creatinine, eGFR, estimated glomerular filtration rate, CR, renal replacement therapy, SUN, serum urea nitrogen.</td>
<td>CIN, RRT, 30-d, 6 mo, all cause mortality, GFR at 2-8 wk postprocedure</td>
</tr>
</tbody>
</table>

Note: Serum Cr in mg/dL may be converted to umol/L by multiplying by 88.4, eGFR in mL/min/1.73 m\(^2\) to mL/s/1.73 m\(^2\) by multiplying by 0.01667.

Abbreviations: CG, Cockcroft-Gault formula; CIN, contrast-induced nephropathy; CR, creatinine; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; RRT, renal replacement therapy; SUN, serum urea nitrogen.

*Trial stopped early because of a greater incidence of CIN in the 0.9% NaCl arm.

†Dose of NAC was 1,200 mg, 2 doses before and after contrast; all other studies that used NAC had a dose of 600 mg, 2 doses before and after contrast.
Change in Bicarbonate Levels

Only 2 studies (n = 188 participants) reported mean change in serum bicarbonate levels at the end of the study period, and bicarbonate levels were higher with sodium bicarbonate compared with normal saline (weighted mean difference, 2.77 mEq/L; 95% CI, 1.94 to 3.61; \( P < 0.001 \)).14,15

Length of Hospital Stay

Sufficient data were not available from the included studies to conduct a meta-analysis.

Sensitivity Analysis

The fixed-effects analysis of the risk of contrast-induced nephropathy from the 12 trials yielded effect sizes similar in magnitude, direc-
tion, and significance to those obtained from random-effects analysis (OR, 0.54; 95% CI, 0.39 to 0.73; \( P < 0.001 \)). The sensitivity analysis of the risk of contrast-induced nephropathy with sodium bicarbonate after exclusion of each individual study 1 at a time yielded effect sizes similar in magnitude and direction to the overall estimates.

The sensitivity analysis of the risk of contrast-induced nephropathy limited to 6 trials that enrolled participants undergoing elective contrast procedures yielded effect sizes (OR, 0.47; 95% CI, 0.24 to 0.90; \( P = 0.02 \)) similar in magnitude and direction to the sensitivity analysis limited to 2 trials in which participants underwent emergency contrast procedures (OR, 0.13; 95% CI, 0.04 to 0.48; \( P = 0.002 \)). The sensitivity analysis limited to 4 trials that included mixed participants undergoing both elective and emergency procedures yielded effect sizes that were similar in direction (OR, 0.84; 95% CI, 0.34 to 2.08; \( P = 0.7 \)), although different in magnitude and statistical significance.

The sensitivity analysis of the risk of contrast-induced nephropathy limited to 7 trials that enrolled participants with estimated glomerular filtration rate less than 60 mL/min/1.73 m\(^2\) yielded effect sizes with sodium bicarbonate (OR, 0.42; 95% CI, 0.22 to 0.79; \( P = 0.007 \)) that were similar in magnitude, direction, and significance to the overall results.

The sensitivity analysis of the risk of contrast-induced nephropathy with sodium bicarbonate limited to the 6 published trials (OR, 0.26; 95% CI, 0.10 to 0.64; \( P = 0.004 \)) yielded risk estimates similar in magnitude, direction, and significance to the overall estimates. The sensitivity analysis of the risk of contrast-induced nephropathy with sodium bicarbonate limited to the 6 trials presented as abstracts yielded effect sizes that were similar in direction (OR, 0.85; 95% CI, 0.46 to 1.57; \( P = 0.6 \)), although different in magnitude and statistical significance (Fig 4).

**DISCUSSION**

In this systematic review of randomized controlled trials, we found a lower incidence of contrast-induced nephropathy with sodium bicarbonate in comparison to hydration using normal saline. Results were similar across trials that included patients who underwent elective or emergency contrast procedures and patients with decreased kidney function. We did not find a significantly increased risk of congestive heart failure or pulmonary edema with sodium bicarbonate–based therapy. We found evidence of publication bias favoring sodium bicarbonate therapy for the prevention of contrast-induced nephropathy.

The precise biological mechanisms that could explain this benefit are uncertain. Renal ischemia and/or oxidative injury with contrast medium administration likely contribute to the develop-
ment of contrast-induced nephropathy.\textsuperscript{29,30} Experimental studies have reported that contrast agents cause direct toxicity to the kidneys through proximal cell vacuolization, interstitial inflammation, and cellular necrosis.\textsuperscript{30,31} Hemodynamic instability and low blood pressure secondary to underlying cardiac disease and the use of such cardioprotective medications as renin-angiotensin system blockers and diuretics could worsen contrast-induced nephropathy.\textsuperscript{32} Sodium bicarbonate decreases the acidification of urine and medulla, which might reduce the generation of free radicals and protect the kidney from injury\textsuperscript{33-35} and thus prevent contrast-induced nephropathy.

Merten et al\textsuperscript{14} tested this hypothesis and reported the results in 2004; subsequently, several trials have been presented/published.\textsuperscript{14-16} We included 12 such trials, and cumulative results showed a reduced incidence of contrast-induced nephropathy with sodium bicarbonate in comparison to normal saline. Several studies have shown that a mild acute decrease in kidney function results in increased length of hospital stay, increased occurrence of chronic kidney disease, greater mortality rates in both the short and long term, and increased health care costs.\textsuperscript{36-40} In this analysis, we did not find a difference in terms of need for renal replacement therapy and inhospital mortality, and this could be attributed to the lack of power of the included studies. These studies were designed to analyze the incidence of contrast-induced nephropathy, rather than the patient-centered outcomes. Based on the available data and our study results, one could argue that this reduction in contrast-induced nephropathy may possibly translate into long-term benefits, but these need to be prospectively studied. Our results from a cumulative analysis of randomized trials do not suggest increased risk of contrast-induced nephropathy with the use of sodium bicarbonate, as recently reported in a single-center retrospective study.\textsuperscript{41}

The safety of hydration with sodium bicarbonate in cardiac patients might be a concern.\textsuperscript{42} Our study results suggest that hydration with sodium bicarbonate is safe in terms of worsening congestive heart failure or the development of acute

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Incidence of contrast-induced nephropathy (CIN) in published versus unpublished studies. Abbreviations: CI, confidence interval; OR, odds ratio.}
\end{figure}
pulmonary edema. This conclusion is bolstered because most participants underwent coronary angiography and thus presumably had high rates of underlying cardiac disease. The change in serum bicarbonate levels at the end of the study period was greater in patients who received sodium bicarbonate therapy, but we could not ascertain whether they sustained metabolic alkalosis from these reports.

Results were similar when analyzed using both fixed- and random-effects models, suggesting the robustness of the analysis. However, our sensitivity and subgroup analysis results should be interpreted with caution. Because most subgroup comparisons are not randomized (but rather observational), the significance of the results should not be overanalyzed. There was a lower incidence of contrast-induced nephropathy with sodium bicarbonate therapy and when sodium bicarbonate was compared with normal saline (without N-acetylcysteine). However, in the subgroup analysis of sodium bicarbonate plus N-acetylcysteine versus normal saline, results were not significant, but were in the same direction as the overall results. This could be attributed to the smaller number of studies and lack of power, rather than a real lack of apparent benefit.

Measures other than hydration, such as prophylactic renal replacement therapy, N-acetylcysteine, and theophylline, have not been shown consistently to be beneficial.43-45 A recently published review analyzed several interventions for the prevention of contrast-induced nephropathy, but included only 1 trial comparing sodium bicarbonate with normal saline.43

Limitations of our meta-analysis include the relative paucity of quality data and the presence of publication bias, in which the significant benefit was limited to published trials. The included trials were of short duration and not adequately powered to measure such patient-centered outcomes as need for dialysis and death. We did not have access to patient-level data to determine whether preexisting decreased kidney function and other risk factors (eg, diabetes and age) could influence the effect of bicarbonate-based hydration on the risk of contrast-induced nephropathy. We could not ascertain whether the most widely used regimen, sodium bicarbonate at 3 mEq/L/h for 1 hour before contrast followed by 1 mEq/L/h for 6 hours after contrast in the emergency setting, was superior to using sodium bicarbonate at 1 mEq/L/h for 12 hours before and after contrast in elective settings. Most studies included in our review analyzed the efficacy of sodium bicarbonate in patients undergoing coronary procedures. Therefore, it may be difficult to generalize these results to patients undergoing other contrast procedures.

We found that the use of bicarbonate-based prophylactic hydration in comparison to normal saline reduced the incidence of contrast-induced nephropathy with no evidence supporting a benefit with regard to such “hard outcomes” as mortality or need for dialysis. It is safe in regard to the occurrence of congestive heart failure. Adequately powered trials that measure patient-oriented outcomes in participants with different underlying risks of contrast-induced nephropathy (patients without and with kidney disease) are needed. These studies should enroll patients undergoing a variety of contrast procedures to compare the effectiveness and safety of sodium bicarbonate-based regimens with other measures. There are several ongoing trials analyzing this unanswered question that might provide more evidence in the future.46 Analysis of currently available data suggests that sodium bicarbonate is an acceptable alternative to normal saline and may be superior for the prevention of contrast-induced nephropathy.

ACKNOWLEDGEMENTS

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