Sodium Bicarbonate Improves Long-Term Clinical Outcomes Compared With Sodium Chloride in Patients With Chronic Kidney Disease Undergoing an Emergent Coronary Procedure

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Background  Contrast-induced nephropathy is associated with increased in-hospital and long-term adverse clinical outcomes.1–3 Also, renal insufficiency is an independent predictor of in-hospital mortality in patients with acute coronary syndrome.4 Previous studies have shown that hydration with sodium bicarbonate prevents contrast-induced nephropathy5–8 However, the effect of sodium bicarbonate on long-term clinical outcomes remains uncertain. To investigate whether hydration with sodium bicarbonate improves long-term clinical outcomes compared with sodium chloride, patients with chronic kidney disease undergoing an emergent coronary procedure were enrolled in a randomized clinical trial with ≥1 year of follow-up. The 59 patients with chronic kidney disease (serum creatinine concentration >1.1 mg/dl or estimated glomerular filtration rate <60 ml/min) were randomly assigned to receive a 154 mmol/L intravenous infusion of either sodium bicarbonate (n=30) or sodium chloride (n=29). The electrolytes were given as a bolus of 3 ml·kg⁻¹·h⁻¹ for 1 h before the administration of contrast, followed by an infusion of 1 ml·kg⁻¹·h⁻¹ for 6 h during and after the procedure. During a mean follow-up period of 15.9±4.5 months, the incidence of renal replacement therapy or death was significantly lower in the sodium bicarbonate group than in the sodium chloride group (3% vs 21%, respectively; p=0.037).

Conclusions  Hydration with sodium bicarbonate reduces the incidence of renal replacement therapy and death in patients with chronic kidney disease undergoing an emergent coronary procedure.

Key Words:  Contrast-induced nephropathy; Contrast media; Sodium bicarbonate

Methods

Study Population
The study protocol and population were described previously.8 In brief, a randomized controlled trial enrolled consecutive eligible patients undergoing an emergent diagnostic or interventional coronary procedure. Eligible patients included individuals aged 20 years or older with renal dysfunction defined as serum creatinine concentration >1.1 mg/dl or estimated glomerular filtration rate <60 ml/min. Exclusion criteria included one of the following: a change in serum creatinine concentration of at least 0.5 mg/dl during the previous 24 h; preexisting dialysis; recent exposure to radiographic contrast media within 2 days of the present study; allergy to radiographic contrast media; pregnancy; or administration of mannitol, fenoldopam, N-acetylcysteine or sodium bicarbonate during the intended time of the present study. Between 7 April 2005 and 3 June 2006, 61 patients were initially enrolled and 59 patients were randomized. The present study was approved by the ethics committee of our institute and written informed consent was obtained from all patients.

Study Protocol
Eligible patients were randomly assigned to the sodium bicarbonate group or the sodium chloride group. Patients allocated to the 2 groups received 154 mmol/L of either sodium bicarbonate or sodium chloride. As soon as possible after admission, the following hydration protocol was started. The initial intravenous bolus was 3 ml·kg⁻¹·h⁻¹ for 1 h, if possible, before the coronary procedure. Patients subsequently received the same fluid at a rate of 1 ml·kg⁻¹·h⁻¹.
during and for 6 h after the procedure. Both fluids were infused on an open label basis. A nonionic, low osmolality contrast media, iopamidol (370 mg/dl), was used in all procedures. The serum creatinine concentration was measured in venous blood at baseline, 2 days and 1 year after the procedure.

Follow-up

As previously reported, there was no difference in baseline and procedural characteristics (Table 1). The incidence of contrast-induced nephropathy, defined as an increase of ≥0.5mg/dl or ≥25% in serum creatinine within 2 days of contrast, was significantly lower in the sodium bicarbonate group than in the sodium chloride group (7% vs 35%, risk ratio 0.19, 95% confidence interval 0.046–0.80, p=0.010).

The primary endpoint was renal replacement therapy (maintenance dialysis or kidney transplant) or death. The study patients were followed up every 1 or 2 months at our heart center for more than 1 year. If a follow-up visit was impossible, then clinical events were determined from reviews of medical records or telephone interviews.

Statistical Analysis

Continuous data are expressed as the mean±SD. Categorical data are presented as absolute values and percentages. Tests for significance were conducted using the t-test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Cumulative rates of events were calculated using the Kaplan–Meier method. Comparison of event-free survival rates between groups was assessed with a 2-sided Mantel–Haenszel (log-rank) test. All analyses were conducted using Stat View version 5.0 (SAS Institute Inc, Cary, NC, USA).

Results

Primary Endpoint

Information on the primary endpoint was available for at least 1 year in all of 59 patients. The mean follow-up period was 16.5±3.5 months in the sodium bicarbonate group and 15.2±5.3 months in the sodium chloride group (p=0.27). Administrations of drugs at discharge were similar between the 2 groups (Table 1). Table 2 shows the number of patients that developed long-term adverse clinical outcomes in the 2 groups. Of 59 patients, 4 patients died during follow-up. The causes of deaths were cerebral infarction (1 patient in the sodium bicarbonate group), gastrointestinal bleeding (1 patient in the sodium chloride group) and in-hospital sepsis (2 patients in the sodium chloride group). Contrast-induced nephropathy was observed in all of 4 patients that died during follow-up and 2 patients that died of sepsis had hemodialysis performed before they developed sepsis. Kaplan–Meier analysis revealed that event-free survival rate was significantly higher in the sodium bicarbonate group than in the sodium chloride group (p=0.037, Fig 1).

Serum Creatinine Concentration

Before the 1-year follow-up, 1 patient in the sodium bicarbonate group and 6 patients in the sodium chloride group died or required maintenance dialysis. There were 5 patients in the sodium bicarbonate group and 2 in the sodium chloride group that did not return for outpatient blood testing during follow-up. Thus, serum creatinine concentration at 1-year follow-up was obtained in only 24

Table 1 Baseline and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sodium bicarbonate</th>
<th>Sodium chloride</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75±8</td>
<td>76±11</td>
<td>0.78</td>
</tr>
<tr>
<td>Men</td>
<td>19 (63%)</td>
<td>17 (59%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>55±10</td>
<td>54±10</td>
<td>0.60</td>
</tr>
<tr>
<td>Serum creatinine concentration (mg/dl)</td>
<td>1.31±0.52</td>
<td>1.32±0.65</td>
<td>0.93</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>57.8±11.6</td>
<td>52.9±12.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10 (33%)</td>
<td>9 (31%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (27%)</td>
<td>10 (35%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>15 (50%)</td>
<td>15 (52%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Volume of contrast media (ml)</td>
<td>112±89</td>
<td>120±61</td>
<td>0.68</td>
</tr>
<tr>
<td>Performed with PCI</td>
<td>16 (53%)</td>
<td>20 (69%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Administration of drugs at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>26 (87%)</td>
<td>27 (93%)</td>
<td>0.41</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>18 (60%)</td>
<td>20 (69%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Statin</td>
<td>6 (20%)</td>
<td>9 (31%)</td>
<td>0.33</td>
</tr>
<tr>
<td>β-blocker</td>
<td>18 (60%)</td>
<td>21 (72%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>11 (37%)</td>
<td>15 (52%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>16 (53%)</td>
<td>17 (59%)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2 Long-Term Adverse Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Sodium bicarbonate</th>
<th>Sodium chloride</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (3%)</td>
<td>3 (10%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>0 (0%)</td>
<td>5 (17%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death or renal replacement therapy</td>
<td>1 (3%)</td>
<td>6 (21%)</td>
<td>0.05</td>
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Anonymous
Contrast-Induced Nephropathy

(80%) patients in the sodium bicarbonate group and 21 (72%) patients in the sodium chloride group. In the patients that did have serum creatinine concentration measured, there was no difference between the 2 groups in baseline and procedural characteristics and administration of drugs at discharge and 1-year follow-up. When blood samples were not available at 1-year follow-up, the most recent serum creatinine concentration was used in the analysis as the 1-year value. In patients that required maintenance dialysis during follow-up, the serum creatinine concentration just before the first dialysis was used in the analysis as the 1-year value. Fig 2 shows serum creatinine concentration at baseline, day 2 and 1 year after contrast administration. In the sodium bicarbonate group, serum creatinine concentration remained unchanged for 1 year (1.31±0.52 to 1.25±0.52 mg/dl, p=NS), although it increased in the sodium chloride group (1.32±0.65 to 1.75±1.25 mg/dl, p=0.015).

Discussion

The present study showed that hydration with sodium bicarbonate reduces the incidence of renal replacement therapy and death in patients with chronic kidney disease undergoing an emergent coronary procedure. This is the first clinical trial to demonstrate that the prevention of contrast-induced nephropathy improves not only short-term but also long-term clinical outcomes.

Persistent Renal Injury and Long-Term Clinical Outcomes

Contrast-induced nephropathy is postulated to occur from free-radical injury9-11. In the renal medulla, hyperosmolar stress and hypoxia caused by contrast media promote free-radical formation12-15. A possible mechanism for the prevention of contrast-induced nephropathy with sodium bicarbonate is inhibition of free-radical renal injury through alkalinizing renal tubular fluid16-19. Renal injury caused by contrast media will continue for just a few days due to the excretion of contrast media. However, in the present study, serum creatinine concentration in the sodium chloride group remained elevated for 1 year. The progression of renal injury in patients with chronic kidney disease is thought to be due to glomerular over-filtration in residual nephrons and the release of neurohormones that reduce renal blood flow. Previous studies reported that the use of contrast media is an independent factor that promotes chronic renal insufficiency and even mild renal insufficiency is associated with a dramatic increase in adverse clinical events, both periprocedurally and during long-term follow-up, in patients undergoing percutaneous interventions2,20. In particular, renal insufficiency is reported to be associated with increased risk of infection, upper gastrointestinal bleeding and cerebral infarction, which were causes of death in the present study21-24.

Thus, we hypothesize that sodium bicarbonate attenuates acute renal injury after exposure to contrast media and improves long-term outcomes by reducing persistent renal insufficiency caused by glomerular over-filtration in residual nephrons and the release of neurohormones that reduce renal blood flow.

Effect of Other Preventive Therapy for Contrast-Induced Nephropathy on Long-Term Clinical Outcomes

Some other prophylactic treatments to prevent contrast-induced nephropathy have recently been used. N-acetylcys-
teine is one of the most commonly used agents to prevent contrast-induced nephropathy. The mechanism of attenuation of renal injury with N-acetylcysteine is believed to be the scavenging of oxygen-derived free radicals in the renal tubule, which is similar to the mechanism of sodium bicarbonate.\(^5^,\)\(^6\) Miner et al previously reported that N-acetylcysteine reduced contrast-induced nephropathy but not clinical events (death, myocardial infarction, dialysis, hospitalization) during 9 months of follow-up.\(^7\) A discrepancy in long-term clinical outcomes between this previous study and the present study may partially be explained by the difference in study populations. The present study enrolled patients undergoing an emergent coronary procedure and hydration was started ≤60 min prior to contrast administration. In contrast, Miner et al enrolled elective cases and hydration was performed for more than 24 h prior to contrast administration, which might reduce the risk of poor clinical outcomes even in the control group. In addition, hydration with sodium bicarbonate may be more effective than N-acetylcysteine for the prevention of contrast-induced nephropathy and result in improved long-term clinical outcomes. According to 2 previous randomized prospective trials, the risk ratios of contrast-induced nephropathy in patients that received sodium bicarbonate ranged from 0.13 to 0.195,\(^8\) In contrast, a review of 9 meta-analyses of randomized prospective trials reported that the risk ratios of contrast-induced nephropathy in patients administered with N-acetylcysteine ranged from 0.37 to 0.73 in 8 meta-analyses and N-acetylcysteine showed no significant beneficial effect in 1 meta-analysis.\(^28\)

**Study Limitations**

The present study has several limitations. Because serum creatinine concentration was not obtained in all patients at 1-year follow-up and information about clinical events were obtained through telephone interview in some patients rather than patient visits, the comprehensiveness of these data may be limited. Although similar drugs were administered at discharge in the 2 groups, some drugs administered during the follow-up period might influence renal function and clinical outcomes. However, among patients that had their serum creatinine concentration measured at 1-year follow-up, there was no difference in drugs administered during the follow-up period. The present study population was small and limited to patients with renal dysfunction undergoing an emergent coronary procedure and the results are from a single institution. A larger multi-center trial including other clinical settings is required to show the beneficial effects of sodium bicarbonate on morbidity and mortality.

**Conclusion**

We demonstrated that hydration with sodium bicarbonate improved not only short-term but also long-term clinical outcomes in patients with chronic kidney disease undergoing an emergent coronary procedure. The results of the present study emphasize the importance of the prevention of contrast-induced nephropathy.

**Acknowledgments**

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**References**


