

Sodium bicarbonate, *N*-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial

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Background Several protective therapies have been developed to prevent contrast-induced nephropathy (CIN). We aimed to investigate the efficacy of sodium bicarbonate by comparing 2 other regimens, including combination of *N*-acetylcysteine (NAC) plus sodium chloride and sodium chloride alone, to prevent CIN in patients undergoing cardiovascular procedures.

Methods We prospectively enrolled 264 patients who were scheduled for cardiovascular procedures and had a baseline creatinine level >1.2 mg/dL. The patients were assigned 1 of 3 prophylactic regimens: infusion of sodium bicarbonate, sodium chloride, sodium chloride plus oral NAC (600 mg bid). Contrast-induced nephropathy was defined as an increase in serum creatinine level >25% or 0.5 mg/dL after 48 hours.

Results There were no significant differences among groups regarding baseline demographic properties and nephropathy risk factors. The change in creatinine clearance was significantly better in the sodium bicarbonate group than other 2 groups ($P = .007$). The incidence of CIN was significantly lower in the sodium bicarbonate group (4.5%) compared with sodium chloride alone (13.6%, $P = .036$) and tended to be lower than in the combination group (12.5%, $P = .059$). After adjusting the Mehran nephropathy risk score, the risk of CIN significantly reduced with sodium bicarbonate compared with sodium chloride alone (adjusted risk ratio 0.29, $P = .043$).

Conclusions Hydration with sodium bicarbonate provides better protection against CIN than the sodium chloride infusion does alone. Combination therapy of NAC plus sodium chloride did not offer additional benefit over hydration with sodium chloride alone. (*Am Heart J* 2007;154:539-44.)

Intravascular administration of contrast media is essential for cardiovascular imaging and percutaneous coronary interventions. However, the increasing incidence of contrast-induced nephropathy (CIN) has become an important problem with the parallel increase in diagnostic and interventional procedures.

Contrast-induced nephropathy is a considerable cause of renal failure, associated with a prolonged hospitalization and significant morbidity and mortality.^{1,2} The most effective treatment strategy for prevention of this serious complication remains to be the preventive measures. Several prevention strategies are being largely investigated in recent years. Fenoldopam, mannitol, and dopamine have been found to be ineffective.³⁻⁵ Pre-procedural hydration remains the most effective and well-known strategy against CIN.^{6,7} However, the optimal fluid regimen is uncertain.

Most of the hydration protocols include the infusion of 0.9% sodium chloride. Oxygen free radicals also play an important role in the pathogenesis of the CIN.⁸ Sodium bicarbonate has antioxidant effects and scavenging reactive free radicals.⁹ Besides this effect, it also

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Submitted March 2, 2007; accepted May 18, 2007.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2007.05.012

Table 1. Baseline demographic and clinical properties of whole study populations and treatment groups and comparison of baseline characteristics among treatment groups

Baseline characteristics	All patients (N = 264)	Sodium chloride (n = 88)	NAC plus sodium chloride (n = 88)	Sodium bicarbonate (n = 88)	P
Age (y)	69 (40-87)	70 (40-84)	67 (48-87)	68 (43-86)	.56
Sex, male (%)	74.6	75	76.1	72.7	.87
BMI (g/m ²)	25.8 (17.2-41.4)	25.7 (19.2-36.1)	25.8 (19.6-41.4)	26 (17.2-36.2)	.84
Contrast dose (mL)	110 (25-300)	110 (30-270)	100 (25-250)	100 (50-300)	.46
Contrast dose (mL/BMI)	3.8 (4.0-4.5)	3.9 (4.1-4.7)	3.7 (3.7-4.5)	3.7 (3.7-4.4)	.44
Creatinine clearance (mL/min)	49.7 (20.5-105.3)	49.8 (21.9-100.9)	45.3 (24-105.3)	52.9 (20.5-80.5)	.57
Serum creatinine (mg/dL)	1.39 (1.2-3.8)	1.40 (1.2-2.3)	1.40 (1.2-2.5)	1.36 (1.2-3.8)	.32
Diabetes mellitus (%)	45.1	47.7	45.5	42.0	.74
Hypertension (%)	77.3	80.7	68.2	75.4	.14
CHF (%)	26.5	23.9	28.4	27.3	.77
PAD (%)	8	8	10.2	5.7	.53
Mehran risk score	9 (1-21)	8 (1-21)	9 (1-20)	8.5 (1-20)	.42
Medications					
ACE inhibitors (%)	69.3	70.5	71.6	65.9	.68
ARB (%)	17	15.9	15.9	19.3	.78
CCB (%)	18.6	12.5	22.7	20.5	.18
β-Blocker (%)	81.4	83	81.8	79.5	.83
Type of procedure					
Coronary angiography (%)	71.4	64.7	68.8	81.3	.55
PCI	28.6	35.3	31.3	18.8	

Values are presented as median (minimum and maximum) value. BMI, Body mass index; CHF, congestive heart failure; PAD, peripheral artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; PCI, percutaneous coronary intervention.

decreases the acidification of urine and renal medulla, which may reduce the generation of free radicals and protects the kidney from oxidant injury.¹⁰ Recently, hydration with sodium bicarbonate has been found to be more effective than those with sodium chloride.^{11,12}

N-acetylcysteine (NAC) is another potential option that reduces the nephrotoxicity of contrast mediums through antioxidant effects.¹³⁻¹⁵ It also enhances the effect of endogenous vasodilator nitric oxide.¹⁵ Some studies revealed successful protective effects of NAC as an adjunct to saline hydration in low-risk patients.^{16,17} However, contradictory results regarding efficacy of NAC were reported, and the protective effect of NAC is equivocal.¹⁸⁻²¹ The direct comparison of sodium bicarbonate and NAC has not been performed previously. We aimed to investigate the comparison of these 2 promising therapies and classic saline infusion regarding nephropathy protective effects before coronary procedures.

Materials and methods

The prospective single-center parallel design trial was conducted to compare the protective efficacy of sodium bicarbonate with 2 other regimens, including combination of NAC plus sodium chloride and sodium chloride alone. Patients were randomly assigned to receive 154 mEq/L of sodium bicarbonate in dextrose solution (n = 88), 154 mEq/L of sodium chloride (n = 88), or 154 mEq/L of sodium chloride plus NAC (n = 88).

Patients

We prospectively enrolled 264 patients who were scheduled for coronary angiography or percutaneous coronary intervention and had a baseline creatinine level >1.2 mg/dL. Exclusion criteria were uncontrolled hypertension (systolic and diastolic blood pressure >160 mm Hg and >110 mm Hg, respectively), emergency catheterization, recent exposure to radiocontrast medium within 2 days, volume overload, and serum creatinine levels >4 mg/dL. No patient received therapy influencing renal function, including fenoldopam, mannitol, dopamine, and theophylline, during the study period.

Study protocol

All patients received the same dose of fluid (1 mL · kg⁻¹ · h⁻¹, upper limit 100 mL/h) for 6 hours before and 6 hours after the procedure. The sodium bicarbonate solution was prepared by adding 154 mL of 1000-mEq/L sodium bicarbonate to 846 mL of 5% dextrose in water. *N*-acetylcysteine was given by oral route 600 mg twice daily. It was begun the day before and continued through the day of the procedure. All types of diuretics were routinely discontinued on the day of the procedure. Serum creatinine and blood urea nitrogen (BUN) levels were measured, and creatinine clearance was calculated according to the Cockcroft-Gault²² equation at baseline and daily for the next 2 days 48 hours after the injection of radiocontrast medium. We also estimated Mehran risk score, reflecting the risk of contrast nephropathy before the procedure. Mehran risk score is calculated according to several risk factors, including dose of contrast media, baseline creatinine clearance, older age, hypotension, heart failure, anemia, and diabetes, as well as the use of intra-aortic balloon pump.²³ Urinary pH was measured to determine the efficacy of sodium

Table II. Comparison of surrogate markers related to CIN among 3 regimens

	Sodium chloride	NAC plus sodium chloride	Sodium bicarbonate	P
Serum creatinine at 48 h (mg/dL)	1.46* (1.0-3.3)	1.42* (0.9-3.7)	1.36 (0.94-3.6)	.006
Creatinine clearance at 48 h (mL/min)	48.1 (17.7-100.9)	46.5 (13.9-127.7)	52.9 (20.4-118.1)	.072
Δ Creatinine (mg/dL)	0.02† (-0.6-1.5)	0.01 (-0.4-2.3)	-0.01 (-0.6-1.89)	.04
Δ Creatinine (%)	1.4† (1.6-10.4)	0.7 (-1-9.8)	-0.8 (-5.1-3.0)	.03
Δ Creatinine clearance (mL/min)	-0.2† (-22.8-13.8)	0* (-23.7-35.7)	1.36 (-23.1-41.4)	.007
Δ Creatinine clearance (%)	-0.58† (-48-52.1)	0 (-62.9-70.4)	3 (-53-77.5)	.013
Δ BUN (mg/dL)	-1.1 (-20-24)	-0.15 (-21-44)	-0.2 (-24.2-28)	.48
Δ BUN (%)	-5.1 (-51.9-95)	-0.6 (-52.9-91.3)	-0.5 (-52.2-72.4)	.27

The differences were arranged between the sodium bicarbonate group and other groups.

**P* < .05.

†*P* < .01.

bicarbonate after the procedure. All patients received the same type of contrast medium, containing low-osmolality ionic contrast agent, ioxaglate (Hexabrix; Guerbet, Cedex, France). Contrast-induced nephropathy was defined as an increase in serum creatinine >25% or 0.5 mg/dL after 48 hours. The primary end point of the study was the development of CIN after the procedure. The secondary end points were the alterations of serum BUN, creatinine values, and creatinine clearance after the procedure.

The study was approved by the ethics committee of Dokuz Eylül University School of Medicine, Izmir, Turkey, as a phase III clinical trial, and written informed consent was obtained from all patients enrolled in the study.

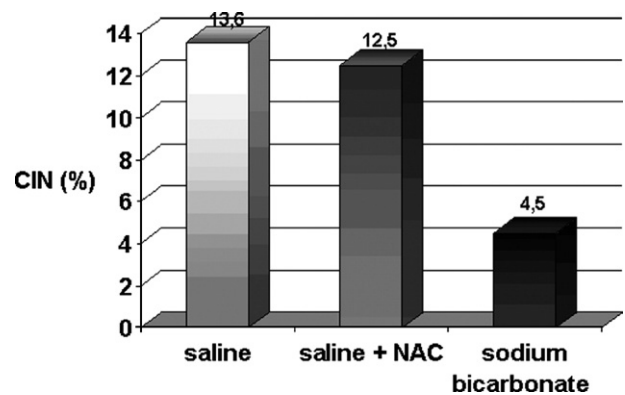
Statistical analysis

All continuous variables were presented as median (minimum and maximum) values. The categorical variables were compared with χ^2 test. All continuous variables were compared with the Wilcoxon rank sum test. The Kruskal-Wallis test was used to compare the 3 groups regarding serum creatinine, creatinine clearance, and other baseline characteristics, as well as delta levels (the differences of values before and after the procedure). The comparison of groups regarding the incidence of CIN and other categorical variables was performed by χ^2 test. Relative risk for the development of CIN was calculated after adjusting Mehran risk score. Logistic regression analysis was used to estimate the adjusted risk ratio (RR) for CIN. All tests were performed as 2-sided. SPSS 11 software (SPSS, Chicago, IL) was used in all statistical procedures.

Results

Most of the study population consisted of coronary heart disease (96.8%). The prevalence of diabetes (45.1%) and heart failure (26.5%) was also high in this study. Baseline median serum creatinine and contrast volume were 1.39 mg/dL and 110 mL subsequently the in whole study population. Baseline characteristics of all patients are shown in the Table I. Of the 264 patients studied, 72% underwent left heart catheterization with coronary angiography alone, and 28% underwent percutaneous coronary intervention.

Figure 1



The comparison of CIN risk among treatment groups.

There were no significant differences among groups regarding age; sex; baseline serum creatinine; creatinine clearance; contrast volume; and the prevalence of diabetes, systolic heart failure, and other clinical risk factors, as well as medications (Table I). The Mehran risk score that estimates CIN risk was also similar among groups (*P* = .42).

The changes in serum creatinine (*P* = .01), creatinine clearance (*P* = .002), and the percentage of changes of these markers (0.009 and 0.004, respectively) after the procedure were found to be lower in the sodium bicarbonate group than in the sodium chloride group (Table II). There was also a significant difference between patients receiving sodium bicarbonate compared with the saline plus NAC group for serum creatinine at 48 hours and changes in creatinine clearance (Table II).

Contrast-induced nephropathy developed in 27 patients in the whole study population (12 patients in the sodium chloride group, 11 patients in the NAC group, and 4 patients in the sodium bicarbonate group).

Table III. Adjusted and unadjusted RRs for the development of CIN in groups

Groups	RR	95% CI	P	Adjusted RR	95% CI	P
Sodium bicarbonate vs sodium chloride	0.30	0.09-0.97	.036	0.29	0.09-0.96	.043
Sodium bicarbonate vs NAC plus sodium chloride	0.33	0.10-1.09	.059	0.34	0.1-1.14	.081
NAC plus sodium chloride vs sodium chloride	0.95	0.37-2.17	.820	0.841	0.34-2.06	.706

There was no statistically significant difference between the 3 treatment arms ($\chi^2 = 4.70$, $df = 2$, $P = .095$). However, when we head-to-head compared each treatment group, the incidence of CIN was significantly lower in the sodium bicarbonate group (4.5%) compared with the sodium chloride group (13.6%, $P = .036$) and tended to be lower than in the NAC group (12.5%, $P = .059$) (Figure 1). There was no significant difference between the NAC and sodium chloride groups regarding incidence of CIN ($P = .82$). After adjusting Mehran risk score, the benefit of the nephropathy risk continued in favor of sodium bicarbonate compared with sodium chloride alone (adjusted RR 0.29, 95% CI 0.09-0.96, $P = .043$); however, the reduced nephropathy risk did not reach significance when comparing NAC plus sodium chloride (adjusted RR 0.34, 95% CI 0.1-1.14, $P = .081$) (Table III). The requirement of hemodialysis developed only in 2 patients (1 from the sodium chloride group, 1 from the sodium bicarbonate group). There was no adverse effect related to active treatments of groups. Congestive heart failure did not occur in all treatment groups after the treatment.

Discussion

We found that hydration with sodium bicarbonate may be the most effective method for protecting the development of CIN compared with NAC and saline infusion. Our study population consisted of patients with moderate nephropathy risk. Median Mehran score was 9, corresponding to the 14% nephropathy risk, and median creatinine value was 1.39 mg/dL, corresponding to the mild renal dysfunction. Sodium bicarbonate infusion significantly reduced the nephropathy risk (71%) compared with saline infusion alone in patients with moderate nephropathy risk. This therapy has also a trend of reducing nephropathy risk (66%) compared with NAC plus saline infusion.

Reviewing the literature, we found 2 studies investigating the protective effect of sodium bicarbonate against CIN in humans.^{11,12} In the first study, hydration with sodium bicarbonate was found to be significantly more effective than hydration with sodium chloride despite the slightly smaller sample size ($n = 60$ vs $n = 88$) and the shorter hydration period compared with our study. Although the duration and rate ($1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 6 hours) of sodium bicarbonate

infusion after the procedure was the same in the 2 studies, initial intravenous therapy ($3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was begun an hour before contrast media injection) was shorter in the previous study. Because a quarter of our population has congestive heart failure, we decided to use lower dosage but longer pretest hydration protocol instead of high-dose bolus. Generally, 24 hours' hydration protocol starting 12 hours before the procedure ($1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) is advised.²⁴ However, this protocol is not possible in emergency situations and is not convenient for patients with heart failure. Despite the different hydration protocols, sodium bicarbonate was more effective than sodium chloride in both studies. Although the incidence of CIN was similar (13.6%-13.6%) in the sodium chloride groups in both studies, the frequency of CIN was higher in the sodium bicarbonate group in our study. The higher prevalence of diabetes, coronary heart disease, and other risk factors in our study may explain the higher incidence of CIN in the sodium bicarbonate group in our study. The exact dose of sodium bicarbonate needed for protection against CIN is a matter of debate.

To the best of our knowledge, this is the first study comparing NAC and sodium bicarbonate for protection from CIN after the cardiovascular procedures and revealing the superior effect of sodium bicarbonate treatment. Although the difference did not reach statistical significance, this situation may be overwhelmed by increasing sample size.

The overall incidence of CIN was reported to be 8% to 28% of patients with baseline renal dysfunction in previous studies using sodium chloride or NAC as a protective regimen.¹⁹ However, the use of sodium bicarbonate reduced the risk of CIN to between 1.7% and 4.5%. In addition, total volume of hydration was lower in both studies that used sodium bicarbonate than the previous studies using sodium chloride. The success of sodium bicarbonate in reducing CIN does not seem to be solely the result of better volume expansion but is consistent with the hypothesis that contrast injury is from free radicals generated within the acid environment of the renal medulla.^{8,9} The protective effect of sodium bicarbonate against CIN in both studies was impressive, and no important side effects were observed because of this medication.

We also considered other risk factors and confounding factors that may increase the nephropathy risk, such as

opaque volume, patient's age, presence of diabetes, previous renal failure, heart failure anemia, and type of contrast medium. We used Mehran risk score to estimate the nephropathy risk. There were no significant differences among groups regarding Mehran score as well as each risk factor. In addition, after adjusting the Mehran risk score, the benefit of sodium bicarbonate still persisted. The type of contrast volume is the same in all groups. Although nonionic iso-osmolar agents provide better protection against CIN in high-risk patients,²⁵ lower thrombotic complications^{26,27} and better clinical results²⁸ were obtained in ionic agents, especially in the coronary interventions. Low osmolar and ionic agents are generally used in cardiovascular procedures. Therefore, we prefer the low-osmolality ionic contrast agent, ioxaglate, which was used routinely in our catheterization laboratory in this study.

We also investigated efficacy of NAC, which is another potential agent reducing the nephropathy risk through antioxidant effects.¹³⁻¹⁵ Previous studies revealed the nephroprotective effect of NAC^{14,15}; however, other studies do not support these findings.^{15,17,29} Finally, NAC therapy claimed to be beneficial in patients having higher nephropathy risk (>11%),²¹ undergoing emergency catheterization and unable to receive saline infusion,^{19,30} and those with previous renal dysfunction. We found that addition of oral NAC therapy to the hydration with sodium chloride did not also offer additional benefit over hydration with sodium chloride alone ($P = .823$). The inefficacy of NAC therapy may be due to several factors, including the presence of adequate saline infusion, mild renal dysfunction, and low opaque volume (median 110 mL), despite the moderate nephropathy risk. On the other hand, sodium bicarbonate was beneficial in the same conditions.

The combination of an infusion of sodium bicarbonate plus NAC may offer more renoprotective effects. The effect of this combination was investigated in a recent study performed in high-risk patients with acute coronary syndromes undergoing emergency percutaneous coronary intervention.¹² Despite this combination being started just before contrast injection, it was found more protective compared with standard therapy with NAC plus saline infusion.

Study limitations

The statistical power of the study, especially regarding the incidence of CIN, may be insufficient because of the small sample size. Although the sample size ($n = 88$ for each group) in this study is same or even higher than other similar studies ($n = 55$ to $n = 88$ ^{11,12}), the requirement of analysis of variance due to the comparison of 3 distinct groups needs a larger sample size to obtain significant results. Finally, our data are limited to 2 days after the procedure. The onset of the CIN may occur later, and consequently, the measuring of the

renal function test within 2 days after the procedure may cause underestimation of the nephropathy risk.

Conclusion

Hydration with sodium bicarbonate provides better protection against CIN than sodium chloride infusion does alone in patients with moderate nephropathy risk. The addition of NAC to sodium chloride infusion did not offer additional benefit over hydration with sodium chloride alone. The efforts for finding the ideal prophylactic treatment against CIN will persist in the future. New combination therapy such as NAC plus sodium bicarbonate is promising, especially in patients undergoing emergency percutaneous coronary intervention. Further studies are required to confirm these outcomes or to investigate. We recommend the use of sodium bicarbonate as a prophylactic treatment before cardiovascular procedures in patients with moderate or high nephropathy risk.

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