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Sodium Bicarbonate Versus Saline for the Prevention of Contrast-Induced Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention

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- Objectives** The purpose of this study was to compare the efficacy of sodium bicarbonate versus isotonic saline in addition to *N*-acetylcysteine (NAC) to prevent contrast-induced nephropathy (CIN) in a larger population of patients with renal dysfunction undergoing coronary angiography or intervention.
- Background** Contrast-induced nephropathy accounts for more than 10% of hospital-acquired renal failure. Recent studies suggest that hydration with sodium bicarbonate is more protective than isotonic saline in the prevention of CIN.
- Methods** The prospective, single center study included 502 patients with estimated creatinine clearance <60 ml/min, randomized to receive infusion of either saline or sodium bicarbonate before and after iso-osmolar contrast medium administration. All patients received oral NAC 600 mg twice a day. Contrast-induced nephropathy was defined as an absolute increase of serum creatinine ≥ 0.5 mg/dl measured within 5 days.
- Results** Contrast-induced nephropathy occurred in 54 patients (10.8%); 25 (10%) were treated with sodium bicarbonate and 29 (11.5%) with saline ($p = 0.60$). In patients with CIN, the mean increase in creatinine was not significantly different in the 2 study groups (0.9 ± 0.6 mg/dl vs. 0.7 ± 0.2 mg/dl, respectively; $p = 0.15$). Only 2 patients needed temporary hemofiltration.
- Conclusions** Hydration with sodium bicarbonate plus NAC before contrast medium exposure is not more effective than hydration with isotonic saline plus NAC for prophylaxis of CIN in patients with moderate-to-severe renal dysfunction. (Sodium Bicarbonate Versus Saline for the Prevention of Contrast-Induced Nephropathy; NCT00606827) (J Am Coll Cardiol 2008;52:599–604) © 2008 by the American College of Cardiology Foundation

Contrast-induced nephropathy (CIN) occurs in up to 15% of patients with chronic renal impairment undergoing diagnostic and therapeutic radiographic procedures (1); 0.5% to 12% (2) of these patients require dialysis and longer hospitalization and show persistent worsening of renal function, possibly expediting the evolution toward end-stage renal failure (1,3–5). Moreover, CIN is associated with an overall higher risk of death (1). The ever-increasing number of contrast-medium–based procedures in high-risk patients makes CIN a relevant possibility in everyday clinical practice.

Several protocols have been tested for the prevention of CIN (6,7), including periprocedural hydration with isotonic or hypotonic saline (8), antioxidant compounds such as

N-acetylcysteine (NAC) (9–12) or ascorbic acid (13), and the use of low- or iso-osmolar contrast agents (14,15), hemofiltration (16), or dialysis (17). The results were often disappointing or inconclusive, and intravenous volume expansion remains to date the only measure of undisputed efficacy.

Recently, 3 randomized studies have compared the effects of sodium bicarbonate versus isotonic saline in humans, resulting in an impressive reduction of CIN in the sodium bicarbonate group, with an incidence <2% (18–20). The objective of the present study was to compare the efficacy of hydration with sodium bicarbonate versus isotonic saline in addition to oral NAC for prophylaxis of CIN in a larger population of patients with chronic kidney dysfunction undergoing planned coronary angiography or intervention.

Methods

Population and study protocol. From January 2005 to March 2006, 1,226 patients underwent planned coronary

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**Abbreviations
and Acronyms**

CI = confidence interval
CIN = contrast-induced nephropathy
NAC = *N*-acetylcysteine
OR = odds ratio

angiographic procedures at our institution; 502 patients with pre-angiographic estimated creatinine clearance <60 ml/min (21) were selected. Figure 1 shows the enrollment criteria and the trial flow. Randomization was performed by computerized open-label assignment in blinded envelopes used in a consecutive fashion; 252 patients were assigned to saline and 250 to bicarbonate. Patients assigned to isotonic saline received 1 ml/kg/h 0.9% sodium chloride for 12 h before and after the procedure (8). Patients in the sodium bicarbonate group (154 mEq/l in dextrose and water) received 3 ml/kg for 1 h before contrast medium, followed by an infusion of 1 ml/kg/h for 6 h after the procedure (18). All patients received 600 mg oral NAC twice a day from the day before to the day after the procedure (9).

Echocardiographic evaluation of left ventricular function was performed in all patients on admission. Hydration rate was reduced to 0.5 ml/kg/h in both arms for patients with left ventricular ejection fraction $<40\%$ or New York Heart Association functional class III–IV.

In all cases, iodixanol (Visipaque, GE Healthcare Ltd., Amersham, United Kingdom), a nonionic, dimeric isosmolar contrast medium, was used.

Serum creatinine concentration was assessed at the time of hospital admission and on days 1, 2, 3, 5, and 10 after the procedure. A further measurement was performed at 1 month in all cases of CIN. All tests were performed in a single, hospital-based laboratory with consistent methodology. Data were recorded in a dedicated database. The protocol was approved by the hospital ethics committee and all patients gave informed consent.

End point of the study and definitions. The primary end point of the study was the development of CIN, defined as an absolute increase of at least 0.5 mg/dl over baseline serum creatinine within 5 days after the administration of the contrast medium (5). Additional end points were: 1) development of CIN, defined as a relative increase $\geq 25\%$ over baseline serum creatinine within 5 days after contrast agent administration; and 2) adverse clinical events, including in-hospital death, acute pulmonary edema, need for dialysis, or hemofiltration.

Renal function was categorized according to the stages set by the National Kidney Foundation (U.S.), with creatinine clearance ≥ 90 ml/min considered normal, 60 to 89 ml/min mildly impaired, 30 to 59 ml/min moderately impaired, and <30 ml/min severely impaired (22). The nephropathy risk score was calculated as specified by Mehran et al. (2). High-contrast load was defined as administered contrast agent volume ≥ 140 ml (23).

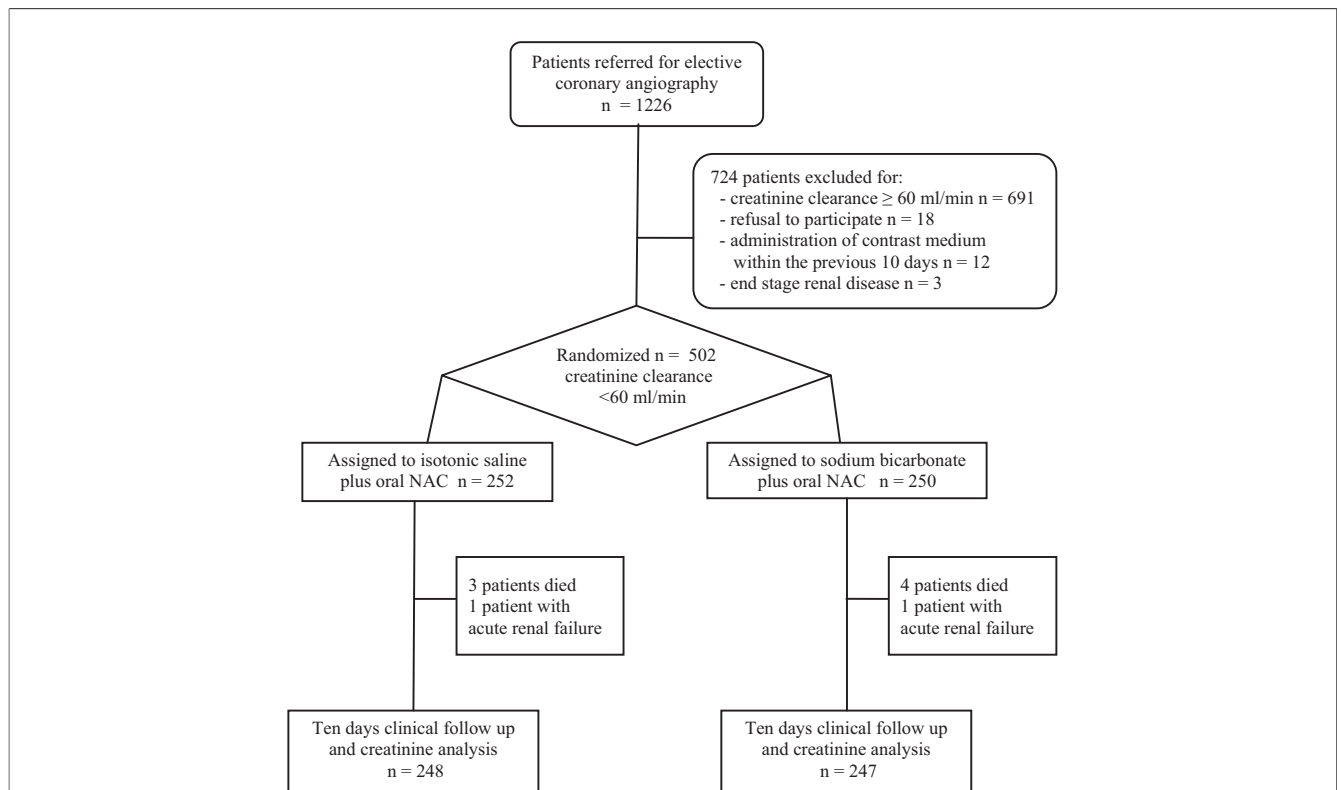


Figure 1 Flow of Patients

The enrollment criteria and the trial flow. NAC = *N*-acetylcysteine.

Table 1 Baseline Clinical, Biochemical, and Procedural Characteristics of Study Patients

	Saline Group (n = 252)	Bicarbonate Group (n = 250)	p Value
Age (yrs)	74 (70-79)	74 (67-79)	0.52*
Female gender	99 (39)	107 (43)	0.42†
Hypertension	143 (57)	147 (59)	0.64†
Diabetes mellitus	59 (23)	62 (25)	0.71†
NYHA functional class III-IV	18 (7)	19 (8)	0.85†
Unstable angina	31 (12)	37 (15)	0.41†
Basal serum creatinine (mg/dl)	1.20 ± 0.3	1.21 ± 0.3	0.61‡
Basal creatinine clearance (ml/min)	42 ± 10	43 ± 11	0.67‡
Basal creatinine clearance <30 ml/min	36 (14)	39 (16)	0.68†
Basal serum urea nitrogen (mg/dl)	49 ± 22	50 ± 20	0.77‡
Basal proteinuria (mg/dl)	8 ± 35	10 ± 31	0.68‡
LV ejection fraction (%)	45 (35-55)	48 (37-55)	0.41*
LV ejection fraction <40%	78 (31)	65 (26)	0.27†
ACE-I or angiotensin-receptor antagonist	91 (36)	106 (42)	0.15†
Diuretic therapy	82 (33)	76 (30)	0.61†
Aspirin	229 (91)	225 (90)	0.85†
Procedure type			0.91†
Coronary angiography	104 (41)	102 (41)	
Elective PCI	148 (59)	148 (59)	
Mean contrast volume administered (ml)	170 (120-230)	160 (120-220)	0.80*
Contrast media volume ≥140 ml	167 (66)	171 (69)	0.56†
Contrast nephropathy risk score	9 (6-11)	9 (6-11)	0.69*
≤5	37 (14)	48 (19)	0.34†
6-10	125 (50)	113 (45)	
11-16	85 (34)	80 (32)	
≥17	5 (2)	9 (4)	

Normally distributed data are presented as mean value ± SD, non-normally distributed data are expressed as median with interquartile range, and categorical data as number (%) of patients. *The values were compared using the Mann-Whitney U test. †The values were compared using the chi-square or Fisher exact test. ‡The values were compared using the unpaired t test.

ACE-I = angiotensin-converting enzyme inhibitor; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; Saline = isotonic sodium chloride.

Statistical analysis. The sample size was calculated by assuming a 15% incidence of the study end point in the isotonic saline hydration group; 500 patients would be required (250 per treatment group) to detect a 50% relative reduction in the incidence of the end point in the sodium bicarbonate group with 90% power at the conventional, 2-sided significance level of 5%.

Categorical variables were presented as counts and percentages and compared by the chi-square or Fisher exact test. Continuous variables were compared by the t test for

normally distributed values; otherwise, the Mann-Whitney U test was used. Multivariate logistic regression analysis was performed using all potentially relevant variables to identify

Table 2 Baseline and Follow-Up Creatinine Concentrations

	Saline Group (n = 252)	Bicarbonate Group (n = 250)	p Value
Baseline creatinine (mg/dl)	1.20 ± 0.3	1.21 ± 0.3	0.61*
Day 1 post-angiography (mg/dl)	1.15 ± 0.3	1.19 ± 0.4	0.23*
Day 2 post-angiography (mg/dl)	1.20 ± 0.4	1.25 ± 0.4	0.14*
Day 3 post-angiography (mg/dl)	1.22 ± 0.4	1.25 ± 0.5	0.44*
Day 5 post-angiography (mg/dl)	1.22 ± 0.4	1.25 ± 0.5	0.55*
Day 10 post-angiography (mg/dl)	1.20 ± 0.3	1.22 ± 0.4	0.67*
Peak creatinine post-angiography (mg/dl)	1.34 ± 0.4	1.37 ± 0.5	0.59*

*The values were compared using the unpaired t test.

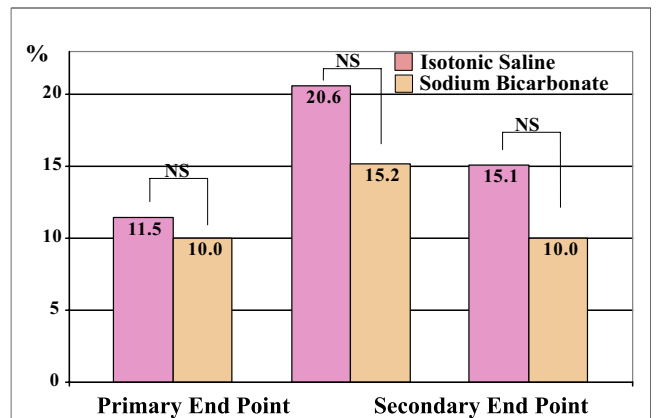


Figure 2 End Points in the Study Groups

Incidence of primary end point (left) (absolute increase of creatinine ≥0.5 mg/dl over baseline value within 5 days after the administration of the radiographic contrast medium). Incidence of secondary end point: relative increase of creatinine ≥25% over baseline value within 5 days (middle) and within 2 days (right) after contrast agent administration. NS = no significant difference.

baseline independent predictors of CIN. All p values are 2-tailed and statistical significance was defined as $p < 0.05$. All analyses were performed with SPSS statistical software, version 13.0 (SPSS Inc., Chicago, Illinois).

Results

Clinical characteristics. No significant differences in baseline clinical, biochemical, and procedural characteristics were found between the 2 groups (Table 1). In particular, higher-risk patients presenting with diabetes, worse baseline renal function, left ventricular dysfunction, or advanced heart failure were evenly distributed. Overall, 15% of patients had severe renal impairment with basal creatinine clearance <30 ml/min.

Contrast-induced nephrotoxicity. Mean creatinine values in the 2 groups are shown in Table 2. In both groups, creatinine significantly increased after contrast medium (baseline vs. peak, $p = 0.001$). The mean absolute increase was not significantly different in the 2 groups (0.14 ± 0.3 mg/dl saline vs. 0.15 ± 0.4 mg/dl bicarbonate, $p = 0.78$). Furthermore, the mean creatinine concentration measured on day 10 was similar in the 2 groups and was not significantly different from the baseline value in each group.

The primary end point of CIN occurred in 54 patients (10.8%): 29 (11.5%) in the saline and 25 (10%) in the sodium bicarbonate group ($p = 0.60$) (Fig. 2, left). No significant difference was observed between the 2 groups, even when CIN was defined as $\geq 25\%$ relative increase in baseline serum creatinine (20.6% saline vs. 15.2% bicarbonate; $p = 0.13$) (Fig. 2, middle). Furthermore, by limiting the analysis to within 48 h, no significant trend favoring the bicarbonate group was observed (10% vs. 15.1%, $p = 0.09$) (Fig. 2, right).

Table 3 shows creatinine values in patients with CIN; no significant differences were found between the 2 groups. At 1 month, creatinine values remained significantly higher than baseline in patients who developed CIN (1.6 ± 0.5 mg/dl vs. 1.4 ± 0.3 mg/dl, respectively; $p = 0.001$) with a

Table 4 Incidence of CIN Among Patients at High Risk for Development of CIN

	Saline Group	Bicarbonate Group	p Value
High and very high contrast nephropathy risk score, ≥ 11	21/90 (23%)	16/89 (18%)	0.38*
Creatinine clearance <30 ml/min	10/36 (28%)	10/39 (26%)	0.83*
Diabetes mellitus	12/59 (20%)	8/62 (13%)	0.27*
Percutaneous coronary intervention	18/148 (12%)	16/148 (11%)	0.71*
Contrast media volume ≥ 140 ml	10/85 (12%)	7/77 (9%)	0.62*

*The values were compared using the chi-square or Fisher exact test.
CIN = contrast-induced nephropathy.

7% reduction in creatinine clearance ($p = 0.014$), without significant differences between the 2 groups.

As expected, the incidence of CIN significantly increased in high-risk patients: 5% in low and moderate nephropathy risk scores versus 21% in high and very high risk scores ($p = 0.001$) and 16.5% in diabetics versus 8.4% in nondiabetics ($p = 0.01$). Table 4 shows the incidence of CIN in high-risk patients.

Clinical events in CIN patients. There were 7 (1.4%) deaths in the entire series of 502 patients: 5 patients died from acute cardiac failure, 1 from infective multiorgan failure, and 1 from sudden death. Of the 7 patients who died, 3 were in the saline group (1.2%) and 4 in the bicarbonate group (1.6%; $p = 0.99$). Of these patients, 6 developed CIN (mortality rate 11.1% in CIN patients vs. 0.2% in non-CIN patients; $p = 0.001$); only 2 patients (1 in each group) were treated with temporary hemofiltration and none required long-term dialysis.

Risk factor analysis. Forward stepwise logistic regression analysis revealed diabetes mellitus (odds ratio [OR]: 2.3, 95% confidence interval [CI]: 1.2 to 4.4; $p = 0.016$), left ventricular ejection fraction (OR: 1.05, 95% CI: 1.03 to 1.08; $p = 0.001$, for every 1-point reduction), and creatinine clearance (OR: 1.07, 95% CI: 1.04 to 1.10; $p = 0.001$, for every 1-ml/min reduction) as independent predictors of CIN in both the saline and the bicarbonate groups.

Discussion

To our knowledge, this is the largest randomized study comparing isotonic saline and sodium bicarbonate in the prophylaxis of CIN. The results suggest that, in patients with moderate-to-severe renal dysfunction, the occurrence of CIN is not significantly different in patients receiving isotonic saline compared with sodium bicarbonate for periprocedural hydration, in addition to oral NAC. Moreover, there was no difference between the 2 treatments also in patients with pre-existing severe renal impairment, diabetes, or high nephropathy risk score.

Alterations in renal hemodynamics and direct tubular toxicity are considered primary factors in the pathogenesis of CIN (4) that lead to a decrease in renal blood flow and glomerular filtration rate. Compromise of renal function

Table 3 Baseline and Follow-Up Creatinine Concentrations in Patients With CIN

	Saline Group (n = 29)	Bicarbonate Group (n = 25)	p Value
Baseline creatinine (mg/dl)	1.38 \pm 0.3	1.42 \pm 0.4	0.65*
Day 1 post-angiography (mg/dl)	1.60 \pm 0.4	1.79 \pm 0.4	0.10*
Day 2 post-angiography (mg/dl)	1.83 \pm 0.5	2.08 \pm 0.5	0.10*
Day 3 post-angiography (mg/dl)	1.87 \pm 0.4	2.04 \pm 0.7	0.31*
Day 5 post-angiography (mg/dl)	1.86 \pm 0.5	1.95 \pm 0.9	0.64*
Day 10 post-angiography (mg/dl)	1.71 \pm 0.4	1.69 \pm 0.5	0.90*
1 month post-angiography (mg/dl)	1.62 \pm 0.4	1.61 \pm 0.6	0.97*
Peak creatinine post-angiography (mg/dl)	2.11 \pm 0.4	2.36 \pm 0.7	0.13*
Mean increase in serum creatinine (mg/dl)	0.73 \pm 0.2	0.94 \pm 0.7	0.15*

*The values were compared using the unpaired t test.
CIN = contrast-induced nephropathy.

increases mortality, length of hospitalization and medical costs, and accelerates end-stage renal disease (3). The results of the present study confirm that CIN is not a benign condition, because it is associated with a significantly higher in-hospital mortality and a significant reduction in the estimated creatinine clearance at 1 month.

We used a single iso-osmolar contrast medium for the entire study to avoid bias and problems of varying responses to different media.

The administration of fluids is the cornerstone treatment to reduce the risk of CIN (6,7). Although the optimal hydration strategy is uncertain, available data support a regimen of 0.9% saline at 1 ml/kg/h intravenously for 12 h before administration of the contrast medium and continuing for up to 12 h after (7).

The prophylactic oral administration of the antioxidant NAC to patients with renal impairment has been investigated on the assumption that reactive oxygen species are involved in CIN. Although some studies suggest that NAC may reduce the incidence of CIN (10), a review of clinical studies by Fishbane et al. (11) has demonstrated mixed results. Therefore, use of NAC, although not recommended for all patients, may be appropriate for patients at very high risk of CIN (24).

If oxygen radicals were involved in the pathogenesis of CIN, hydration with an alkaline solution, such as sodium bicarbonate, might further reduce subsequent renal damage. On this basis, 3 recent studies comparing the results of saline and bicarbonate administration suggest a striking superiority of bicarbonate over saline (18–20). Hydration with bicarbonate showed a very low incidence of CIN (1.7% to 1.9%), notwithstanding the pre-existing finding of severe renal dysfunction (18,19). The study by Merten et al. (18) was terminated early because of a lower-than-expected rate of events in the bicarbonate group, but the timing of the interim analysis and the rules for early termination were not specified in advance (7). Moreover, the hydration protocol with saline was unconventional, which does not allow direct comparisons with other studies. In the REMEDIAL (Renal Insufficiency Following Contrast Media Administration Trial) trial by Briguori et al. (19), the occurrence of CIN was assessed at 48 h, and this could account for an underestimation of CIN. In fact, creatinine usually peaks 4 to 5 days after contrast agent administration (13,25–27). If we had limited the assessment to the first 48 h, we would have missed about 30% of CIN-positive patients (18/54 patients). Still, in the REMEDIAL trial, the incidence of CIN was unexpectedly low (1.9%) in the bicarbonate plus NAC group, significantly lower than in the other treatment arms. In the RENO study by Recio-Mayoral et al. (20), which enrolled patients with acute coronary syndrome who were undergoing emergency percutaneous coronary intervention, a very low CIN incidence was confirmed (1.8%) with bicarbonate.

It is difficult to comment on the marked difference in the results between these previous studies and the present one. Possible explanations include the population size, the extension of creatinine monitoring up to 5 days, and the planned nature of the procedure. However, no definitive explanation can be found. Our data are consistent with the retrospective analysis performed by Schmidt et al. (28) that did not show significant differences between bicarbonate and saline. In any case, the relevant differences in incidence among studies reveal the need for a uniform definition of CIN to be used in clinical practice as well as in research.

Study limitations. The main limitation of our trial was its single center basis. Furthermore, most patients had moderate renal insufficiency and only 15% showed creatinine clearance <30 ml/min. We did not study the effects of bicarbonate on the urine or arterial pH and neither we nor other researchers evaluated the cystatin C levels known to be the most reliable marker of kidney damage, although these levels are influenced by other factors as well.

Conclusions

Hydration with sodium bicarbonate plus oral NAC before contrast medium exposure is not more effective than hydration with isotonic sodium chloride plus oral NAC for prophylaxis of CIN in patients with moderate renal dysfunction. Sodium bicarbonate requires only 1 h of pre-treatment and may represent an option in patients scheduled for urgent agent injection or for outpatient procedures.

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Key Words: contrast-induced nephropathy ■ contrast media ■ angiography ■ angioplasty.

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