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Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL)

A Randomized Comparison of 3 Preventive Strategies

Carlo Briguori, MD, PhD; Flavio Airoldi, MD; Davide D'Andrea, MD; Erminio Bonizzoni, PhD; Nuccia Morici, MD; Amelia Focaccio, MD; Iassen Michev, MD; Matteo Montorfano, MD; Mauro Carlino, MD; John Cosgrave, MD; Bruno Ricciardelli, MD; Antonio Colombo, MD

Background—Volume supplementation by saline infusion combined with *N*-acetylcysteine (NAC) represents an effective strategy to prevent contrast agent–induced nephrotoxicity (CIN). Preliminary data support the concept that sodium bicarbonate and ascorbic acid also may be effective in preventing CIN.

Methods and Results—Three hundred twenty-six consecutive patients with chronic kidney disease, referred to our institutions for coronary and/or peripheral procedures, were randomly assigned to prophylactic administration of 0.9% saline infusion plus NAC ($n=111$), sodium bicarbonate infusion plus NAC ($n=108$), and 0.9% saline plus ascorbic acid plus NAC ($n=107$). All enrolled patients had serum creatinine ≥ 2.0 mg/dL and/or estimated glomerular filtration rate < 40 mL \cdot min⁻¹ \cdot 1.73 m⁻². Contrast nephropathy risk score was calculated in each patient. In all cases, iodixanol (an iso-osmolar, nonionic contrast agent) was administered. The primary end point was an increase of $\geq 25\%$ in the creatinine concentration 48 hours after the procedure (CIN). The amount of contrast media administered (179 ± 102 , 169 ± 92 , and 169 ± 94 mL, respectively; $P=0.69$) and risk scores (9.1 ± 3.4 , 9.5 ± 3.6 , and 9.3 ± 3.6 ; $P=0.21$) were similar in the 3 groups. CIN occurred in 11 of 111 patients (9.9%) in the saline plus NAC group, in 2 of 108 (1.9%) in the bicarbonate plus NAC group ($P=0.019$ by Fisher exact test versus saline plus NAC group), and in 11 of 107 (10.3%) in the saline plus ascorbic acid plus NAC group ($P=1.00$ versus saline plus NAC group).

Conclusions—The strategy of volume supplementation by sodium bicarbonate plus NAC seems to be superior to the combination of normal saline with NAC alone or with the addition of ascorbic acid in preventing CIN in patients at medium to high risk. (*Circulation*. 2007;115:1211-1217.)

Key Words: angiography ■ angioplasty ■ complications ■ contrast media ■ kidney ■ prevention

Radiocontrast media can lead to a reversible form of acute renal failure that becomes apparent soon after the administration of the dye and is generally benign.¹ Transient dialysis may be required, however, especially in high-risk patients.^{2,3} The optimal strategy to prevent contrast agent–induced nephrotoxicity (CIN) remains uncertain. The most recent guidelines⁴ recommend intravenous volume expansion with a saline solution, use of a low- or iso-osmolality contrast agent, and limits on the volume of contrast agent.

Clinical Perspective p 1217

The generation of reactive oxygen species has been considered an important pathophysiological cause of CIN.⁵ *N*-acetylcysteine (NAC) is a potent antioxidant that scav-

enges a wide variety of oxygen-derived free radicals. NAC may prevent CIN by stopping direct oxidative tissue damage and by improving renal hemodynamics.^{6–8} Recently, 2 additional antioxidant strategies have aroused considerable interest: volume supplementation by sodium bicarbonate⁹ and the administration of ascorbic acid.¹⁰ Both approaches should be effective because of their antioxidant properties. We hypothesized that a combination of different antioxidant compounds may give additive benefit in preventing CIN. To test this hypothesis, we performed a prospective, double-blind, randomized study comparing different combinations of antioxidant compounds in patients at medium to high risk for CIN undergoing iso-osmolar contrast agent administration during coronary or peripheral procedures.

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Methods

Patient Population

The present 2-center, randomized, double-blind study compared 3 different strategies for preventing CIN in patients with chronic kidney disease who underwent coronary and/or peripheral angiography and/or angioplasty from January 2005 to August 2006. During this time period, consecutive eligible patients scheduled for coronary and/or peripheral angiography and/or angioplasty were considered for enrollment. Individuals ≥ 18 years of age with stable serum creatinine concentration ≥ 2.0 mg/dL and/or an estimated glomerular filtration rate < 40 mL \cdot min⁻¹ \cdot 1.73 m⁻² were considered eligible for the present study. Estimated glomerular filtration rate was calculated by applying the level-modified Modification of Diet in Renal Disease formula: $(186.3 \times \text{serum creatinine}^{-1.154}) \times (\text{age} - 0.203) \times (0.742 \text{ if female})$.¹¹ Exclusion criteria were serum creatinine levels ≥ 8 mg/dL, a history of dialysis, multiple myeloma, pulmonary edema, acute myocardial infarction, recent exposure to radiographic contrast within 2 days of the study, pregnancy, and administration of theophylline, dopamine, mannitol, or fenoldopam. The local ethics committee approved the study protocol, and all patients gave written informed consent.

Protocol

After enrollment, patients were randomly assigned to 1 of the 3 following treatments: intravenous saline plus NAC administration (saline plus NAC group), intravenous sodium bicarbonate plus NAC administration (bicarbonate plus NAC group), or intravenous saline plus intravenous ascorbic acid plus NAC (saline plus ascorbic acid plus NAC group). All 3 therapies were instituted both before and after administration of the contrast agent. Isotonic saline (0.90%) was given intravenously at a rate of 1 mL/kg body weight per hour (0.5 mL/kg for patients with left ventricular ejection fraction $< 40\%$) for 12 hours before and 12 hours after administration of the contrast agent.^{4,12,13} Patients allocated to the bicarbonate plus NAC group received 154 mEq/L sodium bicarbonate in dextrose and H₂O, according to the protocol reported by Merten et al.⁹ The initial intravenous bolus was 3 mL \cdot kg⁻¹ \cdot h⁻¹ for 1 hour immediately before contrast injection. After this, patients received the same fluid at a rate of 1 mL \cdot kg⁻¹ \cdot h⁻¹ during contrast exposure and for 6 hours after the procedure. Patients allocated to the saline plus ascorbic acid plus NAC group received 3 g ascorbic acid intravenously 2 hours before followed by 2 g the night and the morning after the procedure.¹⁰ We used the intravenous infusion of ascorbic acid because of the low bioavailability after oral administration.

All patients received NAC (Fluimucil, Zambon Group SpA, Milan, Italy) orally at a dose of 1200 mg twice daily on the day before and the day of administration of the contrast agent (total of 2 days).¹⁴ Diuretics were routinely withheld on the day of contrast injection.

Serum creatinine, blood urea nitrogen, sodium, and potassium were measured the day before and 24 and 48 hours after administration of the contrast agent; additional measurements were performed in all cases of deterioration of baseline renal function. The risk score for predicting CIN was calculated according to Mehran et al.¹⁵ Urinary pH was measured at the time of enrollment and during treatment (the morning before contrast media administration in the saline plus NAC group, after infusion of the bolus when the patient spontaneously voided in the bicarbonate plus NAC group, and after the first dose in the saline plus ascorbic acid plus NAC group).

Contrast Agents

Iodixanol (Visipaque, 320 mg iodine/mL, Amersham Health), a nonionic, iso-osmolar (290 mOsm/kg water) contrast agent, was used in all patients. Two different cutoffs were used to identify patients receiving a high-contrast load: ≥ 140 mL¹⁴ and $5 \times$ kilograms of body weight divided by serum creatinine (mg/dL), a weight- and creatinine-adjusted maximum contrast dose.¹⁶ This limit was converted to a dichotomous variable by dividing the actual amount of contrast received by the calculated maximum contrast dose to determine the "contrast ratio." If the ratio was > 1 , then the maximum contrast dose was considered exceeded.¹⁶

Study End Points

The primary outcome measure was development of CIN, defined as an increase in the serum creatinine concentration $\geq 25\%$ from the baseline value at 48 hours after administration of the contrast media or the need for dialysis.⁴ Additional efficacy end points included an increase in the serum creatinine concentration ≥ 0.5 mg/dL at 48 hours after contrast exposure and a decrease of estimated glomerular filtration rate $\geq 25\%$ at 48 hours.

Acute renal failure requiring dialysis was defined as a decrease in renal function necessitating acute hemodialysis, ultrafiltration, or peritoneal dialysis within the first 5 days after intervention.

Statistical Analysis

Treatment assignment among the 3 groups was determined by randomization in a 1:1:1 ratio. To ensure that almost equal numbers of patients receive each of the 3 treatments, a randomization block was used (Plan Procedure of SAS, version 8.2, SAS Institute Inc, Cary, NC). The sample size was selected to demonstrate a reduction in the primary end point of CIN from 15% in the saline plus NAC group^{14,15} to 2% in the bicarbonate plus NAC group and/or saline plus ascorbic acid plus NAC group.⁹ With the use of a 2-sided χ^2 test with a significance level of 0.05, a total of 288 randomized patients gave the study 90% power.

Continuous variables are represented as mean \pm SD or as medians (Q1 to Q3). One-way ANOVA test, the nonparametric Wilcoxon signed rank test for repeated measures, and the Mann-Whitney *U* test for nonrepeated measures were used to determine differences between normal and nonnormally distributed continuous variables, respectively.

Categorical variables were reported as percentages and were analyzed by the χ^2 or Fisher exact test. Treatment comparisons for the primary end point (CIN) were performed with Fisher exact test. To test the impact of preventive therapy strategy (as defined by the study group) on the creatinine level at 48 hours, we used the ANCOVA model after transforming creatinine levels into natural logarithm (to overcome the problem of the nonnormal distribution). In the ANCOVA, we used as covariates the baseline log-creatinine level and the contrast nephropathy risk score. Familywise levels of $P < 0.05$ were considered significant. Multiplicity issues resulting from the pairwise comparisons were approached with the Bonferroni adjustment (yielding a significance threshold of 0.025). Two-tailed unadjusted probability values are reported throughout this article. Data were analyzed with SPSS 11.0 (SPSS Corp, Chicago, Ill) for Windows.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Clinical Characteristics

Between January 2005 and August 2006, 351 patients were randomized to the 3 groups of treatment (Figure 1). A total of 25 patients did not complete the study because they did not have contrast exposure ($n=2$) or they did not have serum creatinine evaluation 48 hours after contrast exposure ($n=23$). In all 23 patients, serum creatinine level was assessed within 1 week after contrast exposure; none have developed clinical renal failure, and the creatinine level available at follow-up did not reach the cutoff of an increase $\geq 25\%$ from the baseline. Therefore, 326 were analyzed: 111 patients in the saline plus NAC group, 108 patients in the bicarbonate plus NAC group, and 107 patients in the saline plus ascorbic acid plus NAC group. One hundred seven patients had coronary angiography alone, 73 underwent ad hoc percutaneous coronary intervention, 96 had scheduled percutaneous coronary intervention, 21 had peripheral angiography, and 27 had peripheral angioplasty. The clinical and biochemical characteristics of the patients in the 3 groups

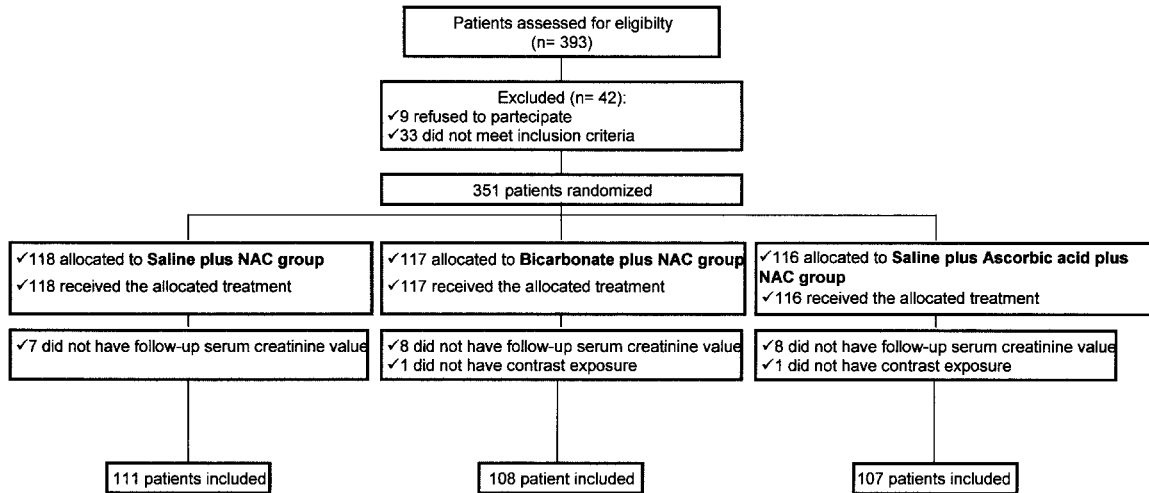


Figure 1. Diagram showing the flow of participants through each stage of the trial.

are shown in Tables 1 and 2. There were no statistically significant differences between groups in the most important clinical and procedural characteristics. Baseline serum creatinine levels, estimated glomerular filtration rate, and incidence of diabetes mellitus were similar in the 3 groups. The total volume of intravenous hydration was lower in the bicarbonate plus NAC group compared with both the saline plus NAC and saline plus ascorbic acid plus NAC groups (bicarbonate plus NAC group, 1081±445 mL; saline plus NAC group, 1562±585 mL; and saline plus ascorbic acid plus NAC group, 1599±584; $P<0.001$). The amount of contrast agent administered was similar in the 3 groups (saline plus NAC group, 179±102 mL; bicarbonate plus NAC group, 169±92 mL; and saline plus ascorbic acid plus NAC group, 169±94 mL; $P=0.69$). A large volume of contrast dye (defined by both >140 mL and contrast ratio >1) was used in >50% of patients in all 3 groups (Table 1). Mean contrast nephropathy risk score was ≈10 in all 3 groups (Table 2). A high (≥11) risk score occurred in 26 of 111 patients (24%) in the saline plus NAC group, in 39 of 108 patients (36%) in the bicarbonate plus NAC group ($P=0.054$ versus saline plus NAC group), and in 27 of 104 patients (26%) in the saline plus ascorbic acid plus NAC group ($P=0.75$ versus saline plus NAC group). Patients receiving sodium bicarbonate experienced urinary alkalinization. In contrast, in patients in the saline plus NAC group and saline plus ascorbic acid plus NAC group, nonsignificant changes in urinary pH were observed (Table 2).

Contrast Agent–Induced Nephrotoxicity

Median serum creatinine concentration for all patients was 1.95 mg/dL (range, 1.80 to 2.28 mg/dL). In all 3 groups, the median serum creatinine concentration decreased significantly from baseline to 48 hours after contrast agent administration ($P<0.05$ for all; Figure 2). The rate of CIN (increase ≥25% of creatinine concentration) was significantly lower in the bicarbonate plus NAC group (2 of 108 patients, 1.9%) than in the saline plus NAC group (11 of 111 patients, 9.9%; $P=0.019$; Table 3). In contrast, the rate of CIN was not statistically different between the saline plus NAC group and saline plus ascorbic acid plus

NAC group (11 of 107, 10.3%; $P=1.00$; Table 3). The additional efficacy end points (ie, an increase ≥0.5 mg/dL in creatinine concentration and a decrease of estimated glomerular filtration rate ≥25% at 48 hours after contrast exposure) also were observed less often in the bicarbonate plus NAC group than in the saline plus NAC group and saline plus ascorbic acid plus NAC group (Table 3). Renal failure requiring temporary dialysis occurred in 1 patient in the saline plus NAC group (0.9%), 1 in the bicarbonate plus NAC group (0.9%), and 4 in the saline plus ascorbic acid plus NAC group (3.8%). A global significant interaction between treatment strategies was observed in the creatinine level 48 hours after adjustment for baseline creatinine level and risk score as covariates ($F=3.85$; $P=0.022$ by ANCOVA model).

Subanalysis of the effectiveness of the 3 preventive strategies was performed according to the following variables: volume of contrast media, risk score, and diabetes mellitus. Rate of CIN was lower in the bicarbonate plus NAC group even in higher-risk subsets (including patients with contrast ratio >1, risk score ≥11, or diabetes mellitus) (Figure 3).

Discussion

The main result of the present study is that the combined administration of sodium bicarbonate plus NAC significantly reduces the risk of CIN in a medium- to high-risk population compared with sodium chloride plus NAC or sodium chloride plus ascorbic acid and NAC.

Contrast media accounts for 10% of all causes of hospital-acquired renal failure.^{1–3} CIN causes a prolonged in-hospital stay and represents a powerful predictor of poor early and late outcome.^{1–3} Careful preprocedural stratification has been recommended. The risk score proposed by Mehran et al¹⁵ is simple to calculate and very useful for individual patient risk assessment. Most patients enrolled in the trial had a medium to high risk score. The mean risk score was ≈10, with an expected 14% risk for CIN. Approximately 30% of our population had a risk score ≥11, with an expected ≥26% risk for CIN.¹⁵ Volume supplementation and the use of a limited amount of low- or iso-osmolality contrast agents are the pivotal recommended strategies for CIN prevention.⁴ In patients at higher risk, additional

TABLE 1. Clinical Characteristics of the Patients in the 3 Groups

	Saline Plus NAC Group (N=111)	Bicarbonate Plus NAC Group (N=108)	Saline Plus Ascorbic Acid Plus NAC Group (N=107)	<i>P</i>
Age, y	71±9	70±9	69±8	0.14
Male, n (%)	90 (81)	95 (88)	84 (78.5)	0.17
Weight, kg	75±12	77±13	77±11	0.26
Height, m	1.66±0.8	1.67±0.9	1.67±0.6	0.22
Body mass index, kg/m ²	27±3	27±4	28±4	0.10
Blood pressure, mm Hg				
Systolic	142±23	140±21	139±21	0.25
Diastolic	77±10	77±11	76±11	0.99
Mean	100±12	98±10	97±12	0.55
LVEF, %	51±10	48±10	50±12	0.16
LVEF <40%, n (%)	12 (11)	19 (18)	18 (17)	0.39
Systemic hypertension, n (%)	96 (86.5)	99 (92)	88 (82)	0.18
Diabetes mellitus, n (%)	61 (55)	53 (49)	63 (59)	0.35
Non-insulin requiring	31 (28)	24 (22)	30 (28)	...
Insulin requiring	30 (27)	29 (27)	33 (31)	...
Peripheral chronic artery disease, n (%)	27 (24.5)	39 (36)	31 (29)	0.14
Drugs, n (%)				
ACE inhibitors	64 (58)	63 (59)	63 (59)	0.97
Calcium channel blocker	43 (38.5)	43 (40)	44 (41)	0.51
Angiotensin II receptor inhibitor	21 (19)	22 (21)	23 (21.5)	0.69
Diuretics	48 (43.5)	46 (42.5)	48 (45)	0.83
β-Blockers	57 (51)	59 (55)	66 (62)	0.18
Statins	82 (74)	78 (72)	85 (79.5)	0.20
Performed procedure, n (%)				
Coronary angiography	34 (30)	39 (36)	34 (32)	0.59
PCI	34 (30)	29 (27)	33 (31)	0.50
Coronary angiography and ad hoc PCI	30 (27)	18 (24)	25 (23.5)	0.18
Peripheral procedures	13 (12)	22 (20)	13 (12)	0.15
Iliac-femoral arteriography	6 (5.5)	9 (8.3)	6 (5.6)	...
Carotid artery angioplasty	4 (3.6)	6 (5.5)	3 (2.8)	...
Femoral artery angioplasty	3 (2.7)	4 (3.7)	3 (2.8)	...
Iliac artery angioplasty	0	3 (2.7)	1 (0.9)	...
Volume of contrast media, mL	179±102	169±92	169±102	0.69
>140 mL, n (%)	70 (63)	56 (52)	57 (55)	0.21
Contrast ratio >1, n (%)	61 (55)	59 (54.5)	66 (63.5)	0.34

Values are mean±SD unless otherwise indicated. LVEF indicates left ventricular ejection fraction; ACE, angiotensin-converting enzyme; and PCI, percutaneous coronary intervention.

efforts should be attempted. Use of NAC, although not recommended, is suggested in this subset of patients.⁴ The combined approach of sodium bicarbonate plus NAC allow us to satisfy the crucial requirement of volume supplementation and administer a potent antioxidant treatment.

Volume Supplementation

Intravascular volume expansion is usually accomplished by isotonic saline.⁴ Volume supplementation prevents CIN mostly by the inhibition of arginine-vasopressin (via vagal inputs from the mechanoreceptors located at the AV junctions and by a direct effect of osmolality on the supra-aortic nuclei)

and the increase in medullary perfusion and regional PO_2 .⁵ In the present study, the total volume of intravenous hydration was lower in the bicarbonate plus NAC group compared with both the saline plus NAC group and saline plus ascorbic acid plus NAC group. This supports the concept that the mechanism of the effectiveness of sodium bicarbonate in preventing CIN is not likely to be a result of a volume expansion larger than that obtained by isotonic saline.

Antioxidant Therapy

The adverse effects of contrast media on renal function may involve the generation of reactive oxygen species, which may

TABLE 2. Biochemical Characteristics of the Patients in the 3 Groups

	Saline Plus NAC Group (N=111)	Bicarbonate Plus NAC Group (N=108)	Saline Plus Ascorbic Acid Plus NAC Group (N=107)	P
Serum creatinine (medians Q1 to Q3), mg/dL				
Baseline	1.95 (1.69 to 2.26)	2.04 (1.88 to 2.36)	1.93 (1.82 to 2.16)	0.33
After 48 h	1.88 (1.54 to 2.36)	1.90 (1.67 to 2.29)	1.88 (1.53 to 2.32)	0.43
eGFR, mL · min ⁻¹ · 1.73 m ⁻²				
40 to 60, n (%)	35 (32)	25 (24)	27 (25)	...
20 to 40, n (%)	68 (62)	72 (78.5)	69 (67.5)	...
<20, n (%)	7 (6)	8 (7.5)	9 (9)	...
Contrast nephropathy risk score				
Score ≤5	19 (17)	14 (13)	11 (10)	...
Score 6 to 10	66 (59)	55 (51)	69 (64.5)	...
Score 11 to 16	25 (23)	34 (31)	21 (19.5)	...
Score >16	1 (1)	5 (5)	6 (6)	...
Serum urea nitrogen, mg/dL				
Baseline	73±29	81±31	78±34	0.23
After 48 h	67±30	64±23	72±39	0.36
Serum sodium, mEq/L				
Baseline	140±4	140±4	141±4	0.44
After 48 h	140±4	140±3	141±4	0.39
Serum potassium, mEq/L				
Baseline	4.8±0.6	4.8±0.6	4.8±0.6	0.28
After 48 h	4.4±0.5	4.4±0.6	4.5±0.5	0.55
Urine volume, mL/24 h				
	1703±746	1485±650	1604±746	0.42
Urine pH				
Baseline	5.3±0.6	5.4±0.6	5.4±0.6	0.90
After treatment	5.6±0.8	6.6±0.9*	5.4±0.5	<0.001

eGFR indicates estimated glomerular filtration rate. To convert serum creatinine to μmol/L, multiply by 88.4.
*P<0.001 vs other groups.

play a role in the effects of various vasoconstrictors.^{5,17-19} Furthermore, medullary hypoxia promotes mitochondrial generation of reactive oxygen species.^{20,21} For this reason, clinical trials have been performed using various antioxidant compounds with the aim of lowering the occurrence of CIN by scavenging reactive oxygen species. Three antioxidant approaches have been investigated in most of the studies: NAC, sodium bicarbonate, and ascorbic acid.

NAC may prevent CIN by stopping direct oxidative tissue damage and by improving renal hemodynamics.⁶⁻⁸ The antioxidant effect of NAC seems to be dose dependent.^{14,22} Although not firmly recommended, NAC administration is suggested especially in high-risk patients.⁴ Free-radical formation is promoted by an acidic environment typical of tubular urine but is inhibited by the higher pH of normal extracellular fluid.^{23,24} It has been hypothesized that alkalin-

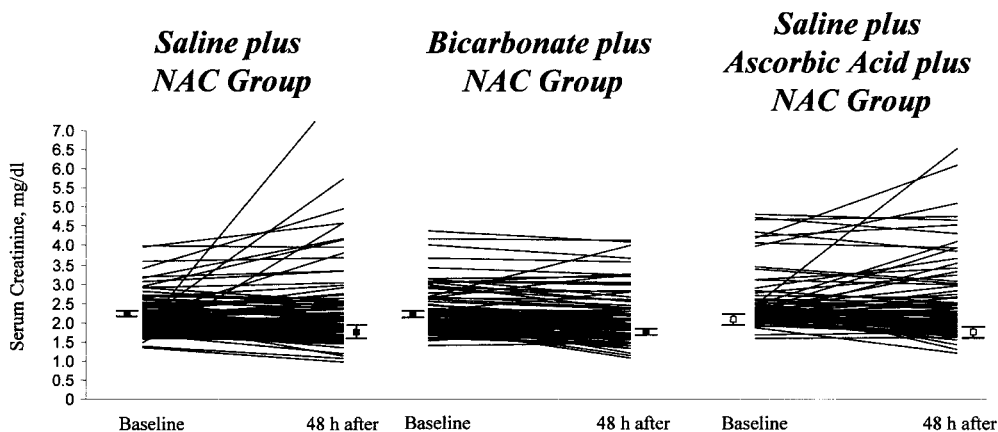


Figure 2. Serum creatinine concentrations before and after contrast administration in the 3 groups. Error bars indicate median.

TABLE 3. Contrast Agent–Enhanced Nephrotoxicity

	Saline Plus NAC Group (N=111), n (%)	Bicarbonate Plus NAC Group (N=108), n (%)	Saline Plus Ascorbic Acid Plus NAC Group (N=107), n (%)	P
Serum creatinine increase by $\geq 25\%$	11 (9.9)	2 (1.9)*	10 (10.3)†	0.010
Serum creatinine increase by ≥ 0.5 mg/dL	12 (10.8)	1 (0.9)‡	12 (11.2)†	0.026
eGFR decrease by $\geq 25\%$	10 (9.2)	1 (0.9)§	10 (10.3)†	0.018

eGFR indicates estimated glomerular filtration rate.

* $P=0.019$, † $P>0.05$, ‡ $P<0.003$, § $P<0.009$ vs saline plus NAC group.

izing renal tubular fluid with bicarbonate²⁵ may reduce injury. At physiological concentrations, bicarbonate scavenges peroxynitrite and other reactive species generated from nitric oxide.²⁶ Additional evidence of the effectiveness of an antioxidant strategy comes from the recent observation by Spargias et al,¹⁰ who investigated the impact of ascorbic acid in preventing CIN. Ascorbic acid is a potent, water-soluble antioxidant capable of scavenging a wide array of reactive oxygen species that can cause damage to macromolecules such as lipids, DNA, and proteins.²⁷ In addition, ascorbic acid can regenerate other antioxidants, acting as a coantioxidant.²⁷

Could the combination of different antioxidant compounds be more effective than a single agent? The results of the present study support this hypothesis within the boundaries of the trial design, which tested the combination of NAC and another antioxidant agent. Therefore, we can recommend that the combined prophylactic strategy of volume supplementation by sodium bicarbonate plus NAC should be used to prevent CIN in patients at medium to high risk undergoing coronary or peripheral procedures. The lack of a favorable protective effect of the combination of ascorbic acid plus NAC compared with NAC alone suggests additional and/or alternative mechanism(s) (other than antioxidant effect), which require further investigation. We may hypothesize that NAC and ascorbic acid work through similar pathways, whereas the protective action of bicarbonate may be different compared with NAC and therefore additive.

The higher amount of HCO_3^- in the proximal convoluted tubule may buffer the higher amount of H^+ as a result of cellular hypoxia and facilitate Na^+ reabsorption through the electrogenic $\text{Na}^+/\text{HCO}_3^-$ cotransporter.²⁸

Study Limitations

The results of the present study cannot be extended to patients at high or very high risk (score ≥ 16) for CIN. Furthermore, we did not test the combination of bicarbonate and ascorbic acid. It has been pointed out that the advantage of NAC administration might be based on a decrease in serum creatinine concentration, reflecting either an increase in creatinine excretion or a decrease in creatinine production.²⁹ On the other hand, Izzedine et al³⁰ reported that a therapeutic dose of NAC did not interfere with serum creatinine assays. We did not measure cystatin C, which seems to be a more reliable marker of renal injury.²⁹

Conclusion

The combined strategy of volume supplementation by sodium bicarbonate plus NAC seems to be superior to the association of normal saline plus NAC alone or plus ascorbic acid and NAC in preventing CIN in patients at medium to high risk.

Disclosures

None.

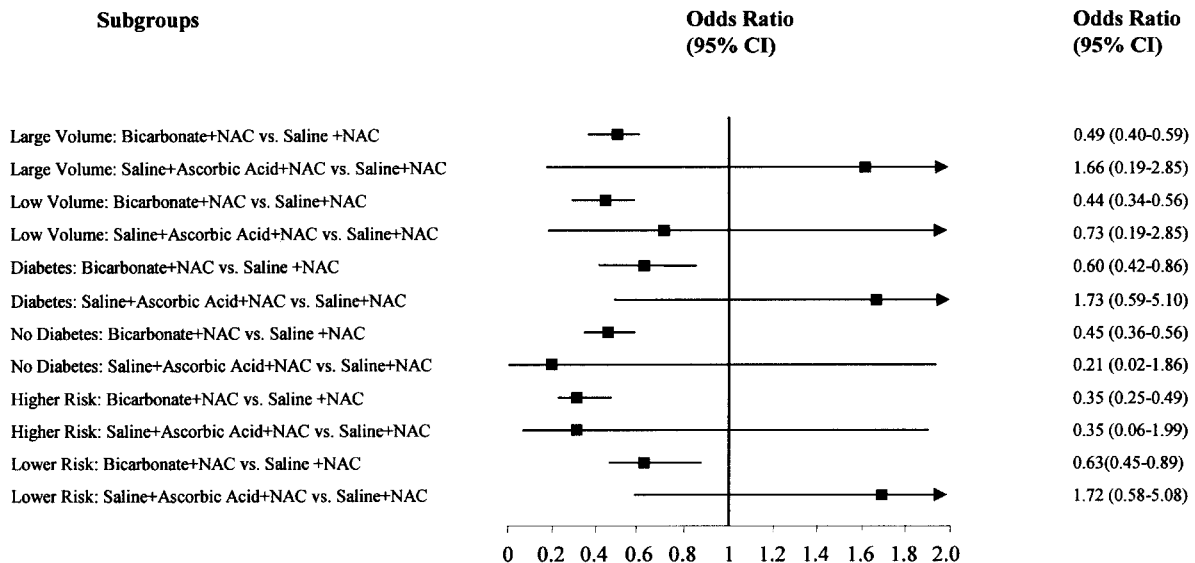


Figure 3. Effect of the 3 preventive approaches in selected subsets according to volume of contrast media, risk score, and presence of diabetes mellitus. Large volume indicates contrast ratio >1 ; higher risk, risk score ≥ 11 . The symbols indicate the unadjusted odds ratios; horizontal lines, 95% CIs.

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CLINICAL PERSPECTIVE

The generation of reactive oxygen species has been considered an important pathophysiological cause of contrast agent-induced nephrotoxicity. We tested whether a combination of different antioxidant compounds may give additive benefit in preventing contrast agent-induced nephrotoxicity. Consecutive patients with chronic kidney disease (serum creatinine ≥ 2.0 mg/dL and/or estimated glomerular filtration rate < 40 mL \cdot min⁻¹ \cdot 1.73 m⁻²) were randomly assigned to prophylactic administration of 0.9% saline infusion plus N-acetylcysteine (NAC; n=111), sodium bicarbonate infusion plus NAC (n=108), and 0.9% saline plus ascorbic acid plus NAC (n=107). Contrast agent-induced nephrotoxicity occurred in 11 of 111 patients (9.9%) in the saline plus NAC group, in 2 of 108 (1.9%) in the bicarbonate plus NAC group ($P=0.019$ versus saline plus NAC group), and in 11 of 107 (10.3%) in the saline plus ascorbic acid plus NAC group ($P=1.00$ versus saline plus NAC group). We can therefore recommend that the combined prophylactic strategy of sodium bicarbonate plus NAC should be used to prevent contrast agent-induced nephrotoxicity in patients at medium to high risk undergoing contrast exposure. The lack of favorable protective effect of the combination of ascorbic acid plus NAC compared with NAC alone suggests additional and/or alternative mechanism(s) (other than antioxidant effect), which require further investigation. We may hypothesize that NAC and ascorbic acid work through similar pathways, whereas the protective action of bicarbonate may be different compared with NAC and therefore additive.

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