N-Acetylcysteine Plus Intravenous Fluids Versus Intravenous Fluids Alone to Prevent Contrast-Induced Nephropathy in Emergency Computed Tomography

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Study objective: We test the hypothesis that N-acetylcysteine plus normal saline solution is more effective than normal saline solution alone in the prevention of contrast-induced nephropathy.

Methods: The design was a randomized, double blind, 2-center, placebo-controlled interventional trial. Inclusion criteria were patients undergoing chest, abdominal, or pelvic computed tomography (CT) scan with intravenous contrast, older than 18 years, and at least one contrast-induced nephropathy risk factor. Exclusion criteria were end-stage renal disease, pregnancy, N-acetylcysteine allergy, or clinical instability. Intervention for the treatment group was N-acetylcysteine 3 g in 500 mL normal saline solution as an intravenous bolus and then 200 mg/hour (67 mL/hour) for up to 24 hours; and for the placebo group was 500 mL normal saline solution and then 67 mL/hour for up to 24 hours. The primary outcome was contrast-induced nephropathy, defined as an increase in creatinine level of 25% or 0.5 mg/dL, measured 48 to 72 hours after CT.

Results: The data safety and monitoring board terminated the study early for futility. Of 399 patients enrolled, 357 (89%) completed follow-up and were included. The N-acetylcysteine plus saline solution group contrast-induced nephropathy rate was 14 of 185 (7.6%) versus 12 of 172 (7.0%) in the normal saline solution only group (absolute risk difference 0.6%; 95% confidence interval −4.8% to 6.0%). The contrast-induced nephropathy rate in patients receiving less than 1 L intravenous fluids in the emergency department (ED) was 19 of 147 (12.9%) versus 7 of 210 (3.3%) for greater than 1 L intravenous fluids (difference 9.6%; 95% confidence interval 3.7% to 15.5%), a 69% risk reduction (odds ratio 0.41; 95% confidence interval 0.21 to 0.80) per liter of intravenous fluids.

Conclusion: We did not find evidence of a benefit for N-acetylcysteine administration to our ED patients undergoing contrast-enhanced CT. However, we did find a significant association between volume of intravenous fluids administered and reduction in contrast-induced nephropathy. [Ann Emerg Med. 2013;62:511-520.]

Please see page 512 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Contrast-induced nephropathy is a decrease in renal function occurring after the administration of radiocontrast material. The cause may be a direct cytotoxic effect of contrast media on renal tubular cells or renal vasoconstriction (with subsequent hypoxia) mediated by perturbations in baseline levels of endogenous vasoactive substances.[1,2] Contrast-induced nephropathy is a leading cause of hospital-acquired renal insufficiency[3] and is associated with an increase in both short- and long-term mortality,[4-8] although the significance of small increases in creatinine level (on the order of 0.5 mg/dL) is debated.

Importance

The use of emergency computed tomography (CT) as a diagnostic tool has increased rapidly,[9] with approximately 18 million emergency CT scans performed in the United States in 2008.[10] The reported rate of contrast-induced nephropathy after emergency contrast-enhanced CT varies significantly by study,[11-23] ranging from 2%[13,16] to 21%.[22] Identifying at-risk patients in the emergency setting has proven difficult, with conflicting data about whether conditions such as chronic kidney disease, older age, congestive heart failure, and anemia are[15,17,19,23] or are not[20,23] risk factors. Beyond the administration of intravenous fluids,[24-27] there is little consensus about the optimal strategy to prevent contrast-

Editor's Capsule Summary

What is already known on this topic

Except for intravenous saline solution administration, little consensus exists about strategies to reduce contrast-induced nephropathy.

What question this study addressed

Does N-acetylcysteine in addition to saline solution administered to patients undergoing intravenous contrast computed tomography (CT) in the emergency department (ED) reduce the rate of contrast-induced nephropathy above that of saline solution administration alone?

What this study adds to our knowledge

N-acetylcysteine did not reduce the rate of contrast-induced nephropathy in the 357-patient target population, but the volume of saline solution infusion was associated with a decrease in contrast-induced nephropathy.

How this is relevant to clinical practice

N-acetylcysteine is not needed as an adjunct to reduce contrast-induced nephropathy among most ED patients undergoing contrast CT, but higher-volume fluid administration was useful.

induced nephropathy. Sodium bicarbonate has been shown to be beneficial in some studies[28,29] but not others,[30,31] with conflicting conclusions among meta-analyses.[32-35] N-acetylcysteine has also had both successes[36-39] and failures.[40-44] Data to guide therapy to prevent contrast-induced nephropathy incurred from contrast-enhanced CT scans performed in emergency department (ED) patients are particularly limited because most contrast-induced nephropathy studies enroll either stable outpatients or patients undergoing emergency cardiac catheterization, neither of which may be representative of emergency patients undergoing CT.

Goals of This Investigation

Given these uncertainties, we sought to study the role of N-acetylcysteine in the prevention of contrast-induced nephropathy in emergency CT by performing a randomized, double-blind, placebo-controlled trial testing the hypothesis that intravenous N-acetylcysteine plus saline solution is superior to intravenous saline solution alone.

MATERIALS AND METHODS

Study Design and Setting

This was a randomized, double-blind, placebo-controlled trial conducted in the EDs at 2 tertiary care, urban university hospitals: Beth Israel Deaconess Medical Center in Boston, MA (adult census >50,000 visits/year), and Carolinas Medical Center in Charlotte, NC (adult census >100,000 visits/year). Randomization was stratified both by study site and whether the clinician intended to use sodium bicarbonate infusion.

Selection of Participants

Patients were eligible for the study if they were undergoing emergency contrast-enhanced CT of the chest, abdomen, or pelvis as part of clinical care, were aged 18 years or older, were willing to have a serum creatinine level measured 48 to 72 hours after CT scan, and had 1 or more risk factors suggesting an elevated risk of contrast-induced nephropathy: preexisting renal dysfunction (creatinine level 1.4 mg/dL or higher or estimated glomerular filtration rate of less than 60 mL/minute per 1.73 m^2),[45] diabetes mellitus, hypertension being treated with antihypertensive medications, coronary artery disease, use of nephrotoxic drugs (cyclosporine A, aminoglycosides, amphotericin, cisplatin, or nonsteroidal anti-inflammatory drugs), liver disease, congestive heart failure (active or by history), older age (65 years of age or older), and anemia (hematocrit level less than 30%). Patients were excluded if they were unable or unwilling to provide written informed consent, had end-stage renal disease currently undergoing regular peritoneal or hemodialysis, were pregnant, had a known allergy to N-acetylcysteine, were judged by the treating physicians to be clinically unstable (30 minute delay for infusion of study medication or placebo was contraindicated), or were being treated with N-acetylcysteine as part of their clinical care. Patients were enrolled primarily during day and evening hours.

Interventions

Patients in the treatment group received 3 g of N-acetylcysteine in 500 mL normal saline solution during 30 minutes before contrast administration. After contrast administration, patients received a continuous infusion of 200 mg of N-acetylcysteine per hour, administered as an infusion of 67 mL per hour of a solution of 3 g of N-acetylcysteine diluted to a total volume of 1,000 mL with normal saline solution. Patients in the placebo group received 500 mL of normal saline solution during 30 minutes before contrast administration and a continuous infusion of 67 mL per hour of normal saline solution after contrast administration. Patients in both arms received the postcontrast infusion (N-acetylcysteine or saline solution) for a minimum of 2 hours. Then, the postcontrast infusion was stopped when one of the following occurred: the patient was discharged from the ED, the post-CT infusion was stopped at the discretion of the clinical team caring for the patient, the patient was discharged from the hospital, or 24 hours elapsed. The postcontrast infusion was also discontinued with the development of any of the following adverse reactions considered severe enough to require discontinuation of the study infusion: symptomatic hypotension requiring treatment, altered mental status, respiratory distress, pulmonary edema, oropharyngeal edema or bronchospasm requiring treatment, severe urticaria or patient discomfort, or any other event

considered severe enough by the clinical team treating the patient to require discontinuation. In such cases, treatment allocation was also unblinded at the request of the clinical team treating the patient. We also recorded and report the development of any new symptoms that occurred temporally with the study infusion (N-acetylcysteine or placebo), regardless of the need to discontinue the infusion.

Outcome Measures

The primary outcome of contrast-induced nephropathy was defined a priori as an increase in serum creatinine level of greater than or equal to 0.5 mg/dL or an increase of 25% above baseline, a commonly used definition.[4,5,28,46] The primary outcome was measured by the change in serum creatinine level from the pre-radiocontrast baseline to the serum creatinine level measured 48 to 72 hours after radiocontrast administration.

Baseline serum creatinine level was measured with a serum sample drawn before radiocontrast administration. To obtain the follow-up sample, inpatients underwent phlebotomy in the hospital; outpatients underwent phlebotomy either by returning to the hospital or during a home visit from an outpatient phlebotomist, with the exception of 1 patient whose blood was drawn at a commercial laboratory.

Secondary outcomes included moderate renal injury (defined as a 100% increase in serum creatinine level) or severe renal failure necessitating renal replacement therapy (peritoneal or hemodialysis). We performed a follow-up telephone call to identify patients who had clinically significant renal injury beyond the 72-hour period.

Anticipating that patients would receive variable amounts of intravenous crystalloid as part of their clinical care in the emergency setting, we abstracted from the chart and recorded the volume of intravenous crystalloid administered within 24 hours of enrollment. We also planned a subanalysis to test the hypothesis that intravenous crystalloid decreases the incidence of contrast-induced nephropathy in a volume-dependent fashion.

Similarly, we also anticipated that patients may receive 1 or more literature-derived prophylactic treatments (such as intravenous fluids) for contrast-induced nephropathy. These clinician-initiated treatments were not excluded by the protocol. We recorded the use of these treatments and these data for inclusion in the planned multivariate analysis.

Sodium bicarbonate is one of the most common clinician-initiated treatments utilized to prevent contrast-induced nephropathy in the emergency setting. To address this potential source of confounding, we used blocked randomization. Although the decision to use sodium bicarbonate was left to the treating physician, if it was used we recommended a standardized dose of 132 mEq sodium bicarbonate in 1 L of 5% dextrose prepared by removing 150 mL of fluid from a 1-L bag of 5% dextrose in water and adding 3 ampules of 8.4% sodium bicarbonate (44 mEq sodium bicarbonate/50 mL solution). We recommended that this solution be infused at 3 mL/kg per hour for 1 hour before radiocontrast administration and then at 1 mL/kg per hour for the 6 hours after contrast administration. A similar (but not identical) regimen has been described previously[47] and is consistent with clinician-initiated treatment protocols available at both institutions.

Finally, because preexisting renal dysfunction is consistently identified as a strong risk factor for contrast-induced nephropathy in other settings, we also planned a subanalysis of patients with a precontrast serum creatinine level 1.4 mg/dL or higher or estimated glomerular filtration rate of less than 60 mL/minute per 1.73 m^2.

Primary Data Analysis

Wald 95% confidence intervals (CIs) for the difference in proportions were used to compare the proportion of patients with contrast-induced nephropathy between study groups. Exclusion of zero in the 95% CI for the difference in proportions is analogous to finding a statistically significant difference between the randomized groups. Logistic regression was performed to compare randomized groups while controlling for important potential confounders. After univariate analysis, we chose a 4-variable model that included age as a summary patient variable, congestive heart failure because there was an uneven distribution during randomization, and intravenous fluids because of its significant association with the primary outcome. Odds ratios are reported, along with their 95% CIs. Data analysis was performed with SAS (version 9.2; SAS Institute, Inc., Cary, NC).

Because the volume of intravenous fluid administration could not be predicted at the outset of treatment in the emergency care setting, we could not adjust our randomization method for it. Instead, to assess the robustness of our hypothesis that increased fluids were associated with a decreased probability of developing contrast-induced nephropathy (and to further guard against unmeasured confounding), we performed a propensity score analysis. We assessed the association of possible confounders with the dependent categorical variable of receiving greater than or equal to 1 L of fluids to create the propensity score. We then calculated the propensity score adjusted odds ratio for the relationship between intravenous fluids (per liter) and the development of contrast-induced nephropathy and compared it with the nonpropensity adjusted odds ratio.

Because the study inclusion criteria included only patients with at least 1 literature-derived risk factor for contrast-induced nephropathy, we initially estimated that the rate of contrast-induced nephropathy would be 20%. We powered the study to find a 50% relative reduction in the rate of contrast-induced nephropathy. To find a 10% absolute risk reduction (50% relative risk reduction) with α=.05 and 90% power, assuming a 20% overall prevalence of contrast-induced nephropathy in the control group and a 10% dropout (lost to follow-up) rate, we initially estimated that we would need 294 patients in each arm (588 patients total) and defined the sample size as 600 patients. At the first interim analysis, the study was repowered to 800 patients at the request of the data and safety monitoring board because of a lower-than-projected event rate of 12% in the control group. Assuming the same 50% relative risk reduction with a 10% dropout rate, with α=0.05 and 80% power (reduced from 90%), the revised estimate called for 784 patients. The sample size was therefore reset to 800 patients.

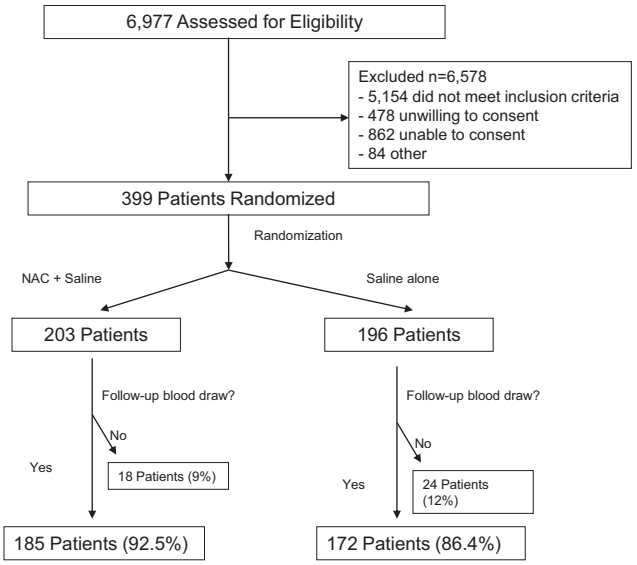

Figure 1. Consort diagram for patient enrollment. *NAC,* N-Acetylcysteine.

We used O'Brien-Fleming stopping criteria for efficacy, with 3 planned interim analyses. In the original analysis plan, significance was defined as follows: 200 patients, $P=0.00058$; 400 patients, $P=0.01506$; and 600 patients, $P=0.04715$. For the revised analysis, we retained the 3 interim analyses with a plan to conduct these at 200 patients, 400 patients, and 800 patients, retaining the same efficacy stopping criteria as above. Stopping for futility or harm was defined at the discretion of the data and safety monitoring board.

The study was approved by the institutional review boards at Beth Israel Deaconess Medical Center and Carolinas Medical Center. All patients enrolled in the study gave written, informed consent. A single data and safety monitoring board was convened to perform a planned analysis of clinical outcomes, morbidity, and mortality at regular intervals of 200 patients.

RESULTS

The study was halted for futility at the second interim analysis by the data and safety monitoring board. The recommendation of the board was that because there was not a strong enough trend toward efficacy, and because the incidence of outcomes was much lower than anticipated, further enrollments would not likely result in an ability to reject the null hypothesis.

Characteristics of Study Subjects

We screened a total of 6,977 patients and enrolled 399 patients in the study (Figure 1), of whom 357 (89.4%) completed a second blood draw to determine outcome and were included in the study. The population was well matched between the treatment and control groups in terms of age, demographics, comorbidities, exposure to contrast agent, and initial renal function (Tables 1 and 2). The baseline serum creatinine level was 1.0 mg/dL (SD 0.3) in both treatment and control groups. The only imbalance in baseline factors was congestive heart failure, which occurred in 4% of the treatment group and 9% of the control group. Both treatment and control groups received moderate intravenous fluid administration in the ED (1,402 [971] versus 1,378 [1,021] mL) (Table 1).

Main Results

The overall rate of contrast-induced nephropathy was 26 of 357 (7.3%). One additional patient who did not have an initial change in creatinine level had detectable renal injury identified during the follow-up telephone call. There were 18 patients in the experimental group (9%) and 24 patients in the control group (12%) who did not complete their second blood draw and were not included in the analysis. The rate of contrast-induced nephropathy in the treatment group of N-acetylcysteine plus saline solution was similar to that of the saline solution alone group (14/185 [7.6%] versus 12/172 [7.0%], for a risk difference of 0.6% [−4.8% to 6.0%]). The absolute change in creatinine level was −0.050 (0.25) versus −0.025 (0.23) (mean difference in groups of 0.025; 95% CI −0.025 to 0.075) (Table 3). Only 1 patient overall (in the N-acetylcysteine plus saline solution group) developed moderate kidney injury, defined as a 100% increase in creatinine level. No patient required renal replacement therapy within the follow-up period.

There were few adverse events, which were self-limited and balanced evenly between the treatment and control groups (Table 4). The adverse reaction was severe enough to require discontinuation of the infusion in only 2 patients (both in the N-acetylcysteine plus saline solution group). No patient developed a severe adverse reaction resulting in death, injury, or prolonged hospitalization.

The total volume of fluid administered in the ED was the only covariate that had an independent association with the reduction of the rate of contrast-induced nephropathy. Although fluid administration in both groups was similar (Figure 2), the rate of contrast-induced nephropathy in patients who received less than 1 L of intravenous fluids was 19 of 147 (12.9%) compared with 7 of 210 (3.3%) in those who received 1 L or more of intravenous fluids, for a risk difference of 9.6% (3.7% to 15.5%) (Figure 3). Our final adjusted model demonstrated that N-acetylcysteine, age, and congestive heart failure did not have a statistically significant association with the development of contrast-induced nephropathy, whereas there was a 69% risk reduction (OR 0.41; 95% CI 0.21 to 0.80) per liter of intravenous fluids administered (Table 5). The c-statistic for model accuracy was 0.67, indicating only a moderate predictive ability for the model. Preexisting renal dysfunction, defined in this study as a creatinine level of 1.4 mg/dL or higher or estimated glomerular filtration rate of less than 60 mL/minute per 1.73 m^2, was not significantly associated with an increased risk of contrast-induced nephropathy.

Because we did not randomize by fluid volume administered, we performed a propensity score adjustment analysis for the

Table 1. Demographics, use of sodium bicarbonate and total fluids by randomized group.*

Parameter	N-Acetylcysteine, N=200	Placebo, N=199
Age, mean (SD) [median; minimum-maximum], y	61.5 (15.3) [62; 28–95]	59.7 (15.9) [59; 18–94]
Sex		
Male	76 (38)	86 (43)
Female	124 (62)	113 (57)
Race		
White	137 (69)	142 (71)
White/Hispanic	1 (1)	0
Black	50 (25)	47 (24)
Asian	1 (1)	2 (1)
Other	11 (6)	8 (4)
Congestive heart failure	7 (4)	18 (9)
CRI, baseline	8 (4)	10 (5)
Coronary artery disease	36 (18)	33 (17)
Myocardial infarction	15 (8)	12 (6)
Diabetes†	65 (33)	64 (32)
Mild DM	51 (26)	48 (24)
Major DM	10 (5)	13 (7)
Hypertension	153 (77)	148 (74)
Liver disease‡	17 (9)	17 (9)
Mild liver disease	8 (4)	5 (3)
Major liver disease	8 (4)	10 (5)
Peripheral vascular disease	7 (4)	5 (3)
Stroke	9 (5)	9 (5)
Reactive airway disease	31 (16)	27 (14)
COPD	14 (7)	13 (7)
Asthma	22 (11)	16 (8)
Malignancy	30 (15)	34 (17)
Solid tumor, no metastasis	20 (10)	14 (7)
Solid tumor, with metastasis	6 (3)	9 (5)
Leukemia or lymphoma	1 (1)	3 (2)
Sodium bicarbonate pretreatment	8 (4.00)	8 (4.02)
Type of IV contrast	193	193
Isovue	12 (6)	13 (7)
Optiray	176 (91)	175 (91)
Visipaque	5 (3)	5 (3)
Volume (in mL) of contrast infused, mean (SD) [median; minimum-maximum]	113.11 (22.95) [130; 65–200]	115.24 (21.06) [130; 25–160]
Total IV fluids plus bolus (in mL) given to administer study medication, mean (SD) [median; minimum-maximum]	1,402 (971) [1,500; 0–5,500]	1,378 (1,021) [1,325; 500–7,100]

IV, Intravenous; *CRI,* Chronic Renal Insufficiency; *DM,* Diabetes Mellitus; *COPD,* Chronic Obstructive Pulmonary Disease.
*Data are presented as No. (%) unless otherwise indicated.
†Major DM is defined as diabetes with the presence of end-organ damage (retinopathy, neuropathy, nephropathy).
‡Minor liver disease is liver disease without ongoing damage (eg, chronic hepatitis C infection); major liver disease is liver disease with ongoing dysfunction or damage (eg, cirrhosis, ascites).

Table 2. Infusion of CT dye and pre- and poststudy CT dye infusion of study medication.

CT Dye and Study Medication Started	N-Acetylcysteine, N=200	Placebo, N=199
Pre-CT dye study medication administered, No. (%)		
Full bolus administered before CT	187 (94)	184 (94)
Bolus not received	6 (3)	3 (2)
Bolus interrupted	5 (3)	4 (2)
Full bolus received after CT	2 (1)	5 (3)
CT dye administered, No. (%)	190 (97)	194 (97)
Postbolus study medication infusion, mean (SD) [median; minimum-maximum], mL	627 (543) [469; 0–1,750]	700 (576) [700; 0–1,650]

tendency to administer more than 1 L of intravenous fluids. We found that 3 factors were associated with reduced fluid administration: age (P=.02), black race (P=.07), and congestive heart failure (P=.05). These factors were used to create a propensity score. After adjusting for our derived propensity score for receiving less than 1 L of fluids, a significant relationship persisted between the amount of fluids administered and the development of contrast-induced

Table 3. Outcomes by randomized group.

Outcome	N-Acetylcysteine, N=185	Placebo, N=172	Mean Difference, (95% CI)*
Baseline creatinine level, mean (SD) [median; minimum-maximum]	1.00 (0.28) [0.9; 0.5 to 1.9]	0.99 (0.27) [0.9; 0.5 to 1.8]	−0.01 (−0.07 to 0.04)
Follow-up creatinine level, mean (SD) [median; minimum-maximum]	0.95 (0.29) [0.9; 0.4 to 2.8]	0.96 (0.31) [0.9; 0.4 to 2.9]	0.01 (−0.05 to 0.07)
Change in creatinine level (follow-up to baseline), mean (SD) [median; minimum-maximum]	−0.050 (0.252) [0; –1.1 to 1.7]	−0.025 (0.227) [0; –1.0 to 1.3]	0.025 (−0.025 to 0.075)
Percentage change in creatinine level, mean (SD) [median; minimum-maximum]	−2.7 (23.4) [0; –61.1 to 154.5]	−1.3 (19.8) [0; –58.9 to 81.3]	1.5 (−3.0 to 6.0)
Increased by 0.5 mg/dL or 25%, No. (%)	14 (7.6)	12 (7.0)	0.6 (−4.8 to 6.0)

*Satterthwaite 95% CIs for the mean difference between groups are summarized for the continuous variables. Wald 95% CIs are reported for the risk difference between groups for the categorical variables.

Table 4. Comparison of adverse events by group.

	No. (%)	
Adverse Event	N-Acetylcysteine, N=200	Placebo, N=199
Itching	1	2 (1.0)
Flushing	3 (1.5)	3 (1.5)
Rash	1 (0.5)	0
Hypotension	0	0
Wheezing	0	1 (0.5)
Nausea	4 (2.0)	4 (2.0)
Vomiting	1 (0.5)	3 (1.5)
Other	3 (2.5)	4 (2.0)

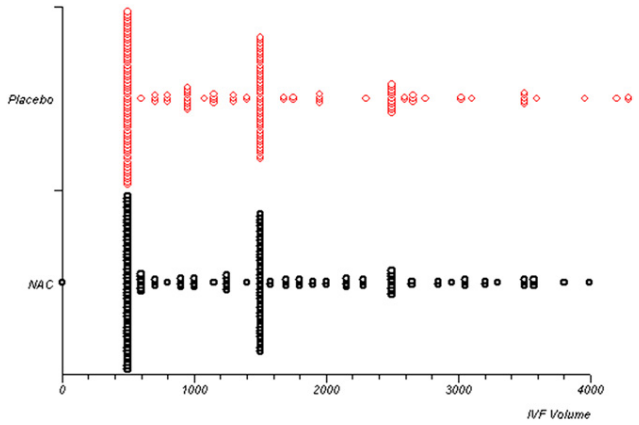

Figure 2. Intravenous fluid administration in placebo (saline solution only) and experimental (N-acetylcysteine plus saline solution) groups. Each circle represents 1 patient. Intravenous fluid volume in milliliters.

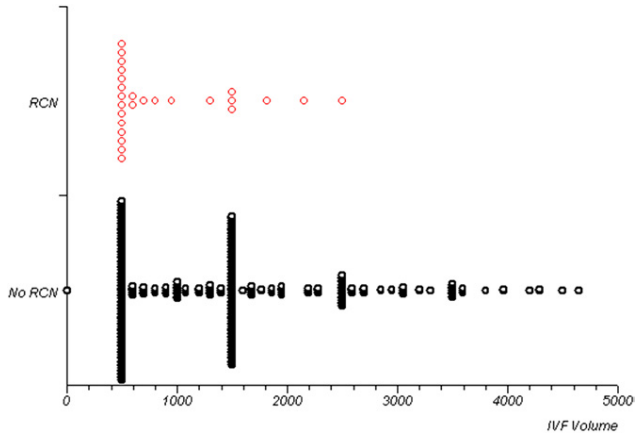

Figure 3. Intravenous fluid administration in contrast-induced nephropathy and noncontrast-induced nephropathy groups. Each circle represents 1 patient. Intravenous fluid volume in milliliters.

Table 5. Final adjusted logistic regression model for the development of contrast-induced nephropathy.

Characteristic	OR	95% CI
Age, in deciles	1.0	0.77–1.30
CHF	1.9	0.48–7.11
IVF, per liter	0.41	0.21–0.80
N-acetylcysteine treatment	1.2	0.51–2.66

CHF, Congestive heart failure.
The c-statistic for the model accuracy was 0.67, and the Hosmer-Lemeshow goodness-of-fit statistic was P=.046, with a χ^2 of 7.72 and df=8.

nephropathy (OR per liter of fluids 0.42; 95% CI 0.21 to 0.82), which was nearly identical to the relationship in our original model without propensity adjustment.

We performed a subgroup analysis on the 87 patients with serum creatinine levels greater than 1.2 mg/dL, a cutoff used in a previous study.[22] In this subgroup, contrast-induced nephropathy occurred in 0% (0/47) of patients treated with N-acetylcysteine plus saline solution and in 7.5% (3/40) of patients treated with saline solution alone, for a risk difference of −7.5% (−15.7% to 0.7%).

LIMITATIONS

Our results were obtained in patients considered to be at relatively low risk for contrast-induced nephropathy and should not be extended to patients who might be at higher risk for it. We purposefully chose our population as we did because previous work has suggested that an elevated serum creatinine

level alone might not identify patients at risk for contrast-induced nephropathy in the emergency setting.[19,23] Our low-risk population had only a 7% incidence of contrast-induced nephropathy by our definition, which was far lower than our initial estimate of 20%, leaving us underpowered to definitively reject our hypothesis. Additionally, we had no patients who developed renal failure, so we cannot comment on this patient-oriented outcome. Thus, although we found no evidence of benefit in our study, it is possible that a much larger study or one with a higher-risk population would yield a different conclusion.

Our study allowed for heterogeneity with respect to total treatment dosages and fluid volumes. In clinical practice, patients treated in an emergency setting may be available for treatment for only a few hours (if discharged) or up to several days (if admitted), and treatments initiated in the emergency setting may be stopped at any time by the admitting service. As such, we believe that our methodology best reflects actual emergency practice and highlights the nationally and internationally recognized need for setting-specific studies.[48]

Serum creatinine level has been criticized as a marker for renal function or injury in contrast-induced nephropathy studies. We chose it to measure the primary outcome of contrast-induced nephropathy for two reasons. First, a change in the level remains the standard for defining contrast-induced nephropathy and other causes of acute kidney injury.

Second, although other markers such as cystatin C, neutrophil gelatinase-associated lipocalcin, or kidney injury molecule 1[49] show some promise as alternatives to serum creatinine, these markers are currently experimental and not available in the clinical setting. At the same time, the inherent limitations of serum creatinine level are particularly important in studies of N-acetylcysteine because there are data demonstrating direct and indirect effects of N-acetylcysteine administration on creatinine measurement and metabolism.[50,51] However, the anticipated nontherapeutic effect of N-acetylcysteine would have increased the likelihood of observing a positive treatment effect, which we did not observe. Furthermore, the effect of N-acetylcysteine on creatinine measurements and metabolism remains highly contested.[50,51]

We report the association between fluid administration and a reduction in contrast-induced nephropathy. This is a finding that is observational, and although we have attempted to address confounding through modeling, including a propensity score analysis, we acknowledge the threat of residual confounding because we did not experimentally assign the administration of fluid. Specifically, despite the multivariate methods, patients who received less fluid may have been sicker (eg, suffered from congestive heart failure), explaining why they received less fluids and have a higher rate of contrast-induced nephropathy.

DISCUSSION

We did not find evidence of benefit in using N-acetylcysteine in addition to intravenous normal saline solution to prevent contrast-induced nephropathy in ED patients undergoing CT imaging with contrast, but we did find a strong association between the degree of fluid administration in the ED and a decrease in the rate of contrast-induced nephropathy. The incidence of contrast-induced nephropathy in our population was low overall (7%), and no patients developed renal failure; thus, these findings are directly generalizable only to a similar low-risk population. The finding of an association between the degree of fluid administration and decreased rate of contrast-induced nephropathy are provocative, but fluid administration was not assigned in an experimental fashion, so this finding should be interpreted in this context.

Unlike many previous studies of both N-acetylcysteine[36-44] and intravenous fluids[24-27] to prevent contrast-induced nephropathy, this study enrolled only emergency CT patients. This is a critical aspect of any study aimed at assessing emergency treatments because commonly accepted approaches to problems outside of the emergency setting may not be applicable to emergency patients. Traditional cardiac risk factors, for example, may have limited ability to risk-stratify patients who present to the ED with chest pain.[52]

Our inability to find a benefit with N-acetylcysteine differs from the result of another, smaller study of emergency CT patients who received 0.45% saline solution and were randomized to no N-acetylcysteine or 900 mg of intravenous N-acetylcysteine both before and after the procedure.[22] The rate of contrast-induced nephropathy, based on serum creatinine level, was 21% in the saline solution only group versus 5% in the N-acetylcysteine plus saline solution group ($P<.03$); there was no difference in contrast-induced nephropathy rates according to cystatin C measurements. That study used 0.45% saline solution rather than 0.9% saline solution for intravenous fluid administration, an important consideration in that 0.9% saline solution appears to be a superior fluid with respect to the prevention of contrast-induced nephropathy.[25]

Our study also differed in baseline serum creatinine values. The previous study required a baseline serum creatinine level greater than 1.2 mg/dL as an enrollment criterion, whereas we had no creatinine minimum. A subgroup analysis of the 87 patients in our study with baseline serum creatinine values greater than 1.2 mg/dL found a lower point estimate for the rate of contrast-induced nephropathy in the N-acetylcysteine plus saline solution group versus the saline solution only group (0% versus 7.5%; risk difference −7.5%; 95% CI −15.6% to 0.7%); however, this subgroup was underpowered for meaningful interpretation. We believe that the specific question of the utility of N-acetylcysteine in patients with mild to moderately increased creatinine levels who undergo ED contrast-enhanced CT deserves further study.

Our data showed a significant, independent association between moderate intravenous fluid administration and a reduction in the rate of contrast-induced nephropathy. Those receiving less than 1 L of fluids developed contrast-induced nephropathy at a rate of 12.9%, versus 3.3% in those who received 1 L or more (risk difference 9.6%; 3.7% to 15.5%).

Although not surprising given the findings of fluid administration in non-ED studies using infusion rates on the order of 1 mL/kg per hour,[24-27] our study supports the concept of moderate fluid administration as a means to reduce the rate of contrast-induced nephropathy specifically in patients undergoing emergency CT.

The only imbalance in baseline factors in our study was congestive heart failure, which occurred in 4% of the treatment group and 9% of the control group. This may have led to a different approach to treatment (eg, less aggressive fluid resuscitation in the congestive heart failure patients in the control group) or a higher propensity to develop contrast-induced nephropathy because of comorbid burden, although it is hard to draw definitive conclusions.

In our study, N-acetylcysteine was safe and associated with a very low rate of adverse events that was similar to that of placebo (Table 4). The adverse event rate of intravenous N-acetylcysteine administered for acetaminophen poisoning varies considerably, ranging from 3.7% to 66% in several studies.[48-51] We used a lower loading dose than these studies (3 g during 30 minutes versus 150 mg/kg during 15 to 60 minutes); we also used a placebo group, whereas many previous studies were observational.

Although we used a common definition of contrast-induced nephropathy (an increase in serum creatinine level of at least 0.5 mg/dL or an increase in serum creatinine level of at least 25% above baseline), the clinical importance of this definition is not entirely clear. For example, in our population of 26 patients who developed contrast-induced nephropathy by this criterion, none subsequently required renal replacement therapy.

In a population of ED patients undergoing contrast-enhanced CT, we found a relatively low rate of contrast-induced nephropathy (7%), and none of these patients developed renal failure. In this population, we were unable to demonstrate that N-acetylcysteine with saline solution was more effective than saline solution alone in preventing contrast-induced nephropathy after emergency contrast-enhanced CT in a low-risk population but found that the administration of 1 L of intravenous fluid or more was associated with a marked decrease in the rate of contrast-induced nephropathy.

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