Journal of Community Hospital Internal Medicine Perspectives

co-action PUBLISHING

RESEARCH ARTICLE

Evaluation of *N*-acetylcysteine for the prevention of contrast-induced nephropathy

Sara K. Richter, PharmD, BCPS[1]* and Andrew J. Crannage, PharmD, BCPS[2]

[1]St. Louis College of Pharmacy, Saint Louis, MO, USA; [2]St. Louis College of Pharmacy and Mercy Hospital St. Louis, Saint Louis, MO, USA

Background: Contrast-induced nephropathy (CIN) remains a leading cause of acute renal failure in hospitalized patients. *N*-Acetylcysteine has been studied previously for the prevention of CIN, resulting in mixed findings.
Objective: The objective of this study was to determine the impact of *N*-acetylcysteine on the development of CIN in order to guide its use at community, teaching hospitals.
Methods: Patients admitted between January 1 and December 31, 2011, receiving intravenous radiocontrast dye were included if they were compliant with two or more of the following conditions: baseline serum creatinine >1.2 mg/dL or estimated creatinine clearance <50 mL/min, age ≥ 75 years, diabetes mellitus, heart failure, or hypertension. The primary outcome was the difference in the proportion of patients in each group (*N*-acetylcysteine or no *N*-acetylcysteine) who developed CIN, which was defined as a ≥ 0.5 mg/dL increase in serum creatinine or a $\geq 25\%$ increase in serum creatinine within 12–96 hours post-exposure to contrast.
Results: A total of 302 patients were included, 151 who received *N*-acetylcysteine and 151 who did not receive *N*-acetylcysteine. Patients who received *N*-acetylcysteine had significantly worse renal function at baseline than those who did not receive *N*-acetylcysteine (mean pre-contrast serum creatinine, 1.41 vs. 0.95 mg/dL, $p<0.0001$). A lower proportion of patients developing CIN was observed between those who received *N*-acetylcysteine and those who did not receive *N*-acetylcysteine (10.2% vs. 21.8%, $p=0.0428$).
Conclusions: The use of *N*-acetylcysteine was likely associated with a reduced incidence of CIN in patients at risk for CIN development. Based on these results, hospitals may benefit from the development of a protocol to guide the appropriate use of *N*-acetylcysteine.

Keywords: *acute kidney injury*; *community hospital*; *prophylaxis*; *nephrotoxicity*; *risk factors*

*Correspondence to: Sara K. Richter, St. Louis College of Pharmacy, 4588 Parkview Place, Saint Louis, Missouri 63110, USA, Email: Sara.Richter@stlcop.edu

Received: 15 January 2015; Revised: 24 March 2015; Accepted: 2 April 2015; Published: 15 June 2015

Contrast-induced nephropathy (CIN) is the third leading cause of acute renal failure in hospitalized patients with an incidence ranging from 2% in low-risk populations to 50% in high-risk populations (1–4). The widely accepted definition of CIN is an absolute (≥ 0.5 mg/dL) or relative ($\geq 25\%$) increase in serum creatinine from baseline after exposure to contrast (3). This increase in serum creatinine is usually transient, with peaks occurring within 3 days after administration of contrast and a return to baseline within 10 days after administration (2).

Commonly referenced risk factors for the development of CIN include underlying chronic renal impairment, heart failure, advanced age, decreased blood volume, concomitant administration of nephrotoxic drugs, and type and higher doses of contrast medium (1, 2, 5). Diabetes mellitus amplifies the risk of CIN in the setting of underlying renal impairment. With these risk factors in mind, tools have been created to help evaluate the risk of CIN in patients undergoing certain procedures (Table 1). The risk level of the patient may help determine the need for prophylaxis in patients requiring contrast.

The pathophysiology behind the development of CIN has not been fully described, but there are three proposed mechanisms: altered renal hemodynamics, direct cytotoxicity, and reactive oxygen species (2, 5). Based on these potential mechanisms, hydration with saline and/or sodium bicarbonate has been studied for the prevention of CIN, and benefit has been seen with these strategies (6, 7). With evidence of damage due to reactive oxygen species, it is thought that the antioxidant, *N*-acetylcysteine, may be able to provide additional benefit in the prevention of CIN by improving renal hemodynamics through vasodilation and by diminishing oxidative stress to the tissue by scavenging oxygen-derived free radicals (1, 3, 8).

Individual studies and meta-analyses on the use of *N*-acetylcysteine for the prevention of CIN show mixed results. Studies in this area are often limited by

Citation: Journal of Community Hospital Internal Medicine Perspectives 2015, **5**: 27297 - http://dx.doi.org/10.3402/jchimp.v5.27297
(page number not for citation purpose)

Table 1. Predicting the risk of an acute decline in kidney function after percutaneous coronary intervention[a]

Risk factor	Score
Systolic pressure <80 mmHg for >1 hour, and patient requires inotropic support or an intra-aortic balloon pump within 24 hours after the procedure	5
Heart failure (New York Heart Association class III or IV), history of pulmonary edema, or both	5
Use of intra-aortic balloon pump	5
Age >75 years	4
Diabetes	3
Hematocrit $<39\%$ for men or $<36\%$ for women	3
Volume of contrast medium	1 for each 100 mL
Serum creatinine level >1.5 mg/dL, or	4
Estimated GFR <60 mL/min/1.73 m^2 body surface area	2, 40 to <60 mL/min/1.73 m^2 4, 20 to 39 mL/min/1.73 m^2 6 <20 mL/min/1.73 m^2

Total risk score	Risk of an increase in serum creatinine levels of >0.5 mg/dL or $>25\%$	Risk of dialysis
	%	
≤ 5	7.5	0.04
6–10	14.0	0.12
11–15	26.1	1.09
≥ 16	57.3	12.6

[a]Adapted from Barrett et al. (2).
GFR = glomerular filtration rate.

small sample size and failure to meet quality standards such as allocation concealment, blinding, and intention-to-treat analysis (8). The first study to report benefit of *N*-acetylcysteine was completed in 2000 (5). In this study, *N*-acetylcysteine in addition to hydration was more effective than hydration alone in patients with chronic kidney disease who received contrast. Following the administration of contrast, the incidence of an elevation in serum creatinine of at least 0.5 mg/dL was 2% in the *N*-acetylcysteine group compared to 21% in the hydration only group ($p = 0.01$) (5). Following this study, additional prospective trials were begun, and results are largely inconsistent (Table 2).

The majority of meta-analyses conducted do show an association between *N*-acetylcysteine use and decreased rates of CIN. Two meta-analyses evaluating eight randomized controlled trials with a total of 885 patients found that *N*-acetylcysteine plus hydration significantly reduced the risk of CIN over hydration alone in patients with chronic renal failure (OR, 0.41; 95% CI 0.22–0.79) (9, 10). The analysis by Alonso et al. (10) only saw benefit in patients with a baseline creatinine <1.9 mg/dL or those given >140 mL of contrast. The largest meta-analysis included 41 studies (n-6379) and showed that *N*-acetylcysteine significantly lowered the risk of CIN over saline alone (RR, 0.62; 95% CI 0.44–0.88) (11).

Results from a large prospective study (n-2308) were published in 2011, after the publication of previously discussed meta-analyses. This study evaluated *N*-acetylcysteine in high-risk patients undergoing vascular angiography. The primary end-point of CIN (defined by a 25% elevation of serum creatinine above baseline 48–96 hours after procedure) occurred in 12.7% of patients receiving *N*-acetylcysteine and 12.7% of patients in the control group. The two groups had identical baseline serum creatinine levels and a near identical rate of elevation, ≥ 0.5 mg/dL in serum creatinine. This non-significant result was noted in all patient subgroups.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines (12) determine their recommendations for CIN prophylaxis based on patient risk. According to the guidelines, alternative imaging methods should be evaluated in any patient considered to be at an increased risk of CIN. If other imaging studies are not obtainable, non-pharmacologic recommendations include using the lowest dose of contrast possible and using low-osmolar contrast media. Pharmacologic prevention recommendations consist of intravenous fluid administration of sodium chloride or sodium bicarbonate. Regarding *N*-acetylcysteine, the KDIGO guidelines suggest using oral *N*-acetylcysteine, in combination with intravenous crystalloids, in patients at increased risk for CIN. The low cost and low incidence of adverse events associated

Citation: Journal of Community Hospital Internal Medicine Perspectives 2015, **5**: 27297 - http://dx.doi.org/10.3402/jchimp.v5.27297

Table 2. Clinical studies on the prophylactic use of *N*-acetylcysteine to prevent CIN[a]

Author	N	Baseline SCr (mg/dL)	*N*-Acetylcysteine dose and route of administration	CIN in the *N*-acetylcysteine group (%)	CIN in the control group (%)	Effect of *N*-acetylcysteine	Volume of contrast dye (mL)
Tepel et al. 2000	83	2.5±1.3	600 mg BID PO, day before and after	2	21	Benefit	75
Diaz-Sandoval et al. 2002	54	1.6±0.4	600 mg BID PO, 1 dose before and 3 after	8	45	Benefit	184±10
Shyu et al. 2002	121	2.8±0.8	400 mg BID PO, day before and after	3.3	24.6	Benefit	117±25
Kay et al. 2003	200	1.25[b] (0.70–3.30)	600 mg BID PO, day before and after	4	12	Benefit	125 (70–320)[b]
Briguori et al. 2002	183	1.5±0.4	600 mg BID PO, day before and after	6.5	11	No Benefit	197±135
Allaqaband et al. 2002	123	2.1±0.8	600 mg BID PO, day before and after	17.7	15.3	No Benefit	125±65
Durham et al. 2002	79	1.6±0.7	1,200 mg BID PO, 1 hour before and 3 hours after	26.3	22	No Benefit	81±39
Webb et al. 2004	447	2.2±0.4	500 mg IV, 1 hour before	7.3	5.7	No Benefit	120 (80–175)[b]
Boccalandro et al. 2003	181	1.8±0.5	600 mg BID PO, day before and after	13	12	No Benefit	191±130
Goldenberg et al. 2004	80	2.0±0.4	600 mg BID PO, day before and after	10	8	No Benefit	116±45
Oldemeyer et al. 2003	96	1.6±0.7	1,500 mg BID PO, day before and after	8.2	6.4	No Benefit	130±72
Baker et al. 2003	80	1.8±0.5	150 mg/kg over 30 min immediately before and 50 mg/kg over 4 hours	5	21	Benefit	230±158
Miner et al. 2004	180	1.4±0.6	2,000 mg PO, 1 dose before and 2 doses after	9.6	22.2	Benefit	347±199
Sar et al. 2010	45	0.53±0.15	1,200 mg BID PO, day before and after	0	15	Benefit	NR
Amini et al. 2009	90	≥1.5	600 mg BID PO, day before and after	11.1	14.3	No Benefit	118±35
Coyle et al. 2006	137	1.14±0.43	600 mg BID PO, day before and after	9.2	1.4	No Benefit	98±35
Gomes et al. 2005	156	≥1.5	600 mg BID PO, day before and after	10.4	10.1	No Benefit	102±47

[a]Adapted from Briguori et al. (4).
[b]Median (interquartile range).
CIN = contrast-induced nephropathy, SCr = serum creatinine, PO = by mouth, BID = two times daily, NR = not reported.

with *N*-acetylcysteine form the basis of their recommendation, while recognizing varying results regarding efficacy. Other organizations provide different recommendations for the prevention of CIN. For example, the American College of Cardiology Foundation/American Heart Association Task Force does not recommend the use of *N*-acetylcysteine. Instead, they prefer adequate hydration alone (13).

Due to increases in costs, in-hospital mortality, and hospital stay associated with CIN, further evaluation of its incidence is warranted (1, 2, 5). The objective of this study was to determine the impact of *N*-acetylcysteine on the development of CIN to guide its use.

Methods

Study design

This study was a historical cohort conducted at a 1,000 bed community, teaching hospital. There was no funding received for the study, and all data collection and analysis

was completed by the primary author. The study protocol was approved by the appropriate institutional review boards.

Study population

Patients who had received intravenous contrast in 2011 were screened, via use of a random number generator, for inclusion into the study. Patients who met inclusion criteria had at least two of the following characteristics: baseline serum creatinine ≥ 1.2 mg/dL or a creatinine clearance < 50 mL/min (calculated via Cockcroft–Gault equation), age > 75 years, diabetes mellitus noted in their past medical history, systolic heart failure with documented ejection fraction $< 40\%$, and/or hypertension evidenced by their past medical history or active use of antihypertensives. In addition, patients had to have a serum creatinine level drawn at baseline (within 1 month prior to receiving contrast) and within 12–96 hours following contrast administration. Excluded patients were those < 18 years of age, those who were pregnant or breast feeding, and those who were receiving dialysis prior to or during the study period.

Procedure

Patients were identified through electronic prescription numbers in the electronic medical record. A list of all patients who received intravenous contrast during the defined study period was generated. From this list, an additional filter was added to separate patients who had also received *N*-acetylcysteine from patients who had not received *N*-acetylcysteine. Patients from these two lists (those who received *N*-acetylcysteine and those who did not) were selected randomly. Data on patients included in these two groups were then collected and analyzed (Fig. 1).

Outcomes

The primary outcome was the absolute difference in the proportion of patients who developed CIN with and without the administration of *N*-acetylcysteine. CIN was defined as a ≥ 0.5 mg/dL increase in serum creatinine or a $\geq 25\%$ increase in serum creatinine within 12–96 hours post-exposure to contrast.

Secondary outcomes included sub-analysis of the primary outcome according to patients with diabetes mellitus, patients aged > 75 years, patients with systolic heart failure, and patients with hypotension (systolic blood pressure < 90 mmHg) immediately prior to contrast administration; absolute difference in blood urea nitrogen (BUN) post-exposure to contrast; and proportion of patients with an elevation in serum creatinine of at least 0.3 mg/dL.

Statistical analysis

The primary hypothesis was that *N*-acetylcysteine would reduce the incidence of CIN. On the basis of reported rates of CIN in previous studies, the anticipated incidence of CIN without *N*-acetylcysteine was 15%. For the primary outcome, we determined that 302 patients would provide a power of 80% to detect a 10% absolute risk reduction (ARR) with a two-sided alpha level of 0.05. Categorical data were analyzed using the Fisher's Exact Test. Continuous data were analyzed using the Student's t-test.

Results

Patient characteristics

Baseline characteristics are presented in Table 3. Approximately 45% of patients were aged ≥ 75. The majority of patients had co-morbidities of diabetes and/or hypertension, with more patients with diabetes present in the group not receiving *N*-acetylcysteine compared to the group that did receive *N*-acetylcysteine. When comparing baseline renal function, mean pre-contrast serum creatinine in patients receiving *N*-acetylcysteine was 1.41 mg/dL compared to 0.95 mg/dL in those not receiving *N*-acetylcysteine ($p = 0.0001$).

Primary outcome

CIN occurred in 14 (9.3%) patients who received *N*-acetylcysteine and in 27 (17.9%) patients who did not (ARR 8.6%, $p = 0.0428$) (Table 4). The mean increase in serum creatinine post-contrast in patients receiving *N*-acetylcysteine and patients not receiving *N*-acetylcysteine

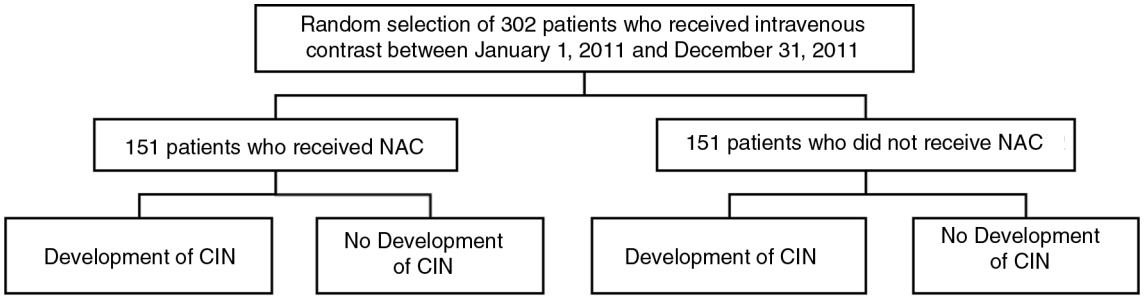

Fig. 1. Study procedure.
CIN = contrast-induced nephropathy, NAC = *N*-acetylcysteine.

Table 3. Baseline characteristics

Characteristic	*N*-Acetylcysteine ($n=151$)	No *N*-acetylcysteine ($n=151$)	*p*
Mean age (years)	70.19 ± 11.43	70.66 ± 12.45	0.7291
Gender-male, *n* (%)	85 (0.56)	78 (0.52)	0.4886
Mean height (inches)	67.0 ± 4.2	66.6 ± 4.0	0.4652
Mean weight (kg)	89.9 ± 26.4	87.9 ± 24.8	0.5057
Mean IBW (kg)	64.0 ± 11.4	63.0 ± 10.9	0.4353
Age ≥75, *n* (%)	62 (0.41)	75 (0.50)	0.1653
Diabetes, *n* (%)	66 (0.44)	88 (0.58)	0.0155
Hypertension, *n* (%)	140 (0.93)	145 (0.96)	0.3182
Congestive heart failure, *n* (%)	22 (0.15)	19 (0.13)	0.7372
Hypotension prior to contrast, *n* (%)	4 (0.03)	3 (0.02)	1.0000
Mean pre-contrast SCr (mg/dL)	1.41 ± 0.55	0.95 ± 0.62	0.0001
Mean hours prior to contrast – SCr (mg/dL)	11.37 ± 22.41	12.06 ± 30.67	0.8238
Mean hours post-contrast – SCr (mg/dL)	40.97 ± 27.23	38.21 ± 25.24	0.3609
Mean pre-contrast CrCl (mL/min)	46.30 ± 19.97	68.18 ± 30.96	0.0001
Mean pre-contrast BUN (mg/dL)	29.34 ± 14.15	18.78 ± 9.67	0.0001

SCr = serum creatinine, CrCl = creatinine clearance (as estimated by Cockcroft–Gault), BUN = blood urea nitrogen, IBW = ideal body weight.

was 0.07 and 0.05 mg/dL, respectively. Of the 41 patients who developed CIN, 16 met both criteria in the definition of CIN. Twenty-four patients met the definition solely based on a relative increase in serum creatinine of ≥25%, and one patient met the definition solely based on an absolute increase in serum creatinine of ≥0.5 mg/dL.

Secondary outcomes

Secondary outcomes are presented in Table 4. In a subgroup analysis of the primary outcome, significant differences in the incidence of CIN were seen in patients aged at least 75 years and in patients with a history of hypertension. A significant difference was also noted in the percent change in BUN.

Fluid administration

In the overall population ($n=302$), 77% of patients received fluids either prior to or immediately following contrast administration; however, the mean percentage was different between the two study groups. In the group of patients receiving *N*-acetylcysteine, 85% of patients received fluids compared to only 69% of patients in the group that did not receive *N*-acetylcysteine. Seventy patients did not receive any fluids around the time of contrast administration. Patients who received fluids had a lower incidence of CIN than patients who did not receive fluids (10.8% vs. 22.9%, respectively; $p=0.0157$). The effect of fluid administration in the overall population, in those receiving *N*-acetylcysteine ($p=0.0411$), and in those not receiving *N*-acetylcysteine ($p=0.2561$), is presented in Fig. 2.

Discussion

In this historical cohort, we evaluated the use of *N*-acetylcysteine for the prevention of CIN. Based on the primary outcome, *N*-acetylcysteine is likely associated with a lower incidence of CIN.

Table 4. Outcomes

Outcome	*N*-Acetylcysteine ($n=151$)	No *N*-acetylcysteine ($n=151$)	*p*
Development of CIN, *n* (%)	14/151 (9.3)	27/151 (17.9)	0.0428
Patients ≥75 years, *n* (%)	4/62 (6.5)	16/75 (21.3)	0.0156
Diabetes mellitus, *n* (%)	8/66 (12.1)	16/88 (18.2)	0.3725
Hypertension, *n* (%)	11/139 (7.9)	26/145 (17.9)	0.0134
Heart failure, *n* (%)	3/22 (13.6)	6/19 (31.6)	0.2595
Hypotension prior to contrast, *n* (%)	1/4 (25.0)	1/3 (33.3)	1.0000
Increase in SCr ≥0.3 mg/dL, *n* (%)	17 (11.3)	15 (9.9)	0.8520
Absolute change in BUN (mg/dL)	0.61	1.17	0.6366
Percent change in BUN (%)	3.3	13.7	0.0307

CIN = contrast-induced nephropathy, BUN = blood urea nitrogen, SCr = serum creatinine.

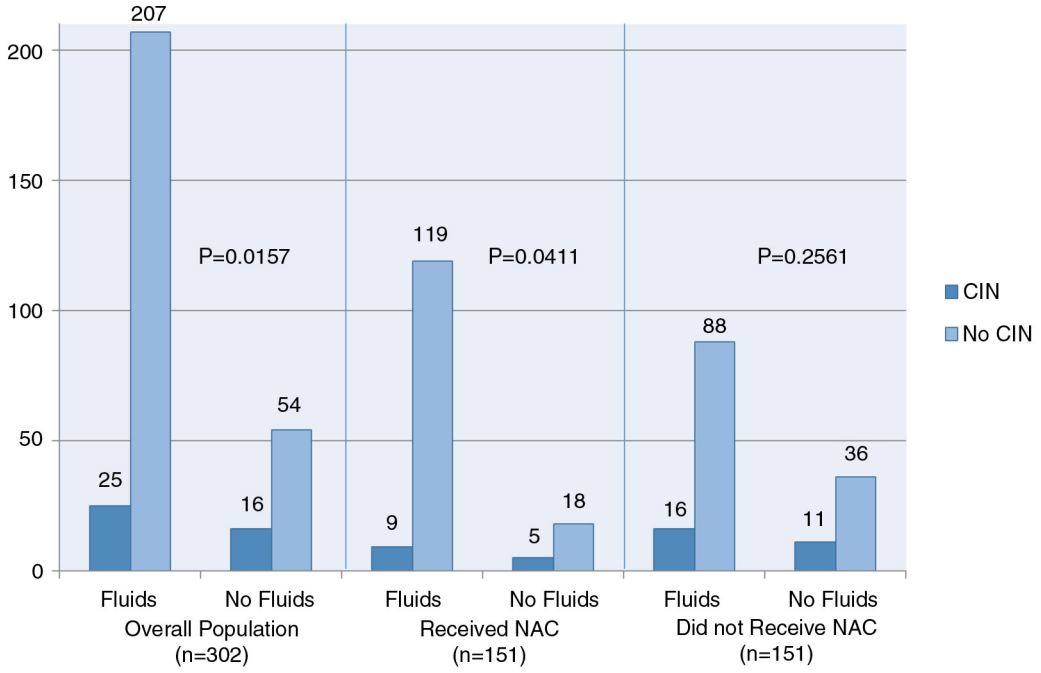

Fig. 2. Effect of fluids.
CIN = contrast-induced nephropathy, NAC = *N*-acetylcysteine.

Patients included in this cohort had to have at least two risk factors for the development of CIN. Based on the predictive risk tool by Barrett et al. (2), the majority of patients in this cohort would have been at a 7.5–14% risk of developing CIN by our definition. The incidence of CIN in patients not receiving *N*-acetylcysteine was approximately 18%, which is just above the average incidence in previously reported studies (15.7%) (4). Similarly, in patients who did receive *N*-acetylcysteine, the incidence of CIN in our study was similar to the average incidence reported in previous literature (4) (9.3% vs. 8.9%, respectively). This suggests that patients reviewed in this study were at similar baseline risk to those patients reviewed by others previously.

In addition, this study analyzed the effect of fluids, both with regard to use and non-use of *N*-acetylcysteine, since adequate hydration has been shown to be effective in preventing CIN. The definition of CIN and the risk factors for CIN used in this study are well agreed upon in the literature. In addition to the primary outcome being analyzed with a commonly accepted definition of CIN, other important markers used to describe acute kidney injury and CIN were included as secondary outcomes (absolute change in serum creatinine and change in BUN) (14, 15).

There were several limitations to this study. First, the retrospective nature of the study does not allow for cause and effect relationships to be analyzed, and we are only able to support an association between the incidence of CIN and *N*-acetylcysteine use. Second, the dose, route, and frequency of *N*-acetylcysteine were not analyzed in this study. All patients who received *N*-acetylcysteine received at least 600 mg/dose and received at least a total of four doses surrounding contrast administration, but no consistent pattern of administration was enforced. For example, some patients received one dose of *N*-acetylcysteine before contrast and three after, while others received two doses before and three after, and so on. This is a potential confounder as previous literature suggests that certain dosing strategies may be associated with better outcomes (16, 17). Selection bias is a factor due to patients in the group receiving *N*-acetylcysteine having worse renal function at baseline. This is likely reflective of healthcare professionals being more likely to order *N*-acetylcysteine in patients with poor renal function at baseline due to the potential benefit seen in previous literature.

Several additional confounders may be present in this study. The concomitant use of nephrotoxic medications by patients was not taken into account. In addition, there was an observed difference in the percentage of patients in each group that received intravenous fluids. Since fluids are considered the first-line preventative strategy for CIN, the difference in use could impact the results of this study. Finally, while the study did meet power for the primary outcome, it is possible that the non-significant results noted in some subgroups is a result of type II error.

Despite the limitations presented above, this study may provide information that can be used for the prevention of CIN. In this time of nationwide drug shortages,

the appropriate utilization of medications is of extreme importance. Based on the subgroup analysis of the primary outcome, a protocol can be developed that takes into account the patients at the highest risk for CIN development. In addition to helping identify those at the highest risk, a protocol could help with the establishment of more consistent *N*-acetylcysteine dosing. Developing this type of protocol would likely reduce drug cost and allow *N*-acetylcysteine to be used more resourcefully.

This study conducted in a community, teaching hospital may provide information to healthcare professionals in numerous health-system settings. Specifically, other community-based hospitals can use the data presented here to tailor or develop *N*-acetylcysteine protocols. While this study was retrospective, the inclusion of over 300 patients allows for extrapolation to other hospitals. Future prospective studies, analyzing a larger number of patients with various risk factors, would help in the development of a protocol for the optimal use of *N*-acetylcysteine. Ideally, these future studies would take into account confounding factors such as the use of nephrotoxic drugs and the dosing strategy of *N*-acetylcysteine.

Conclusion

In conclusion, *N*-acetylcysteine was likely associated with a lower rate of CIN in patients at risk for CIN development. Subgroup analyses reveal patients who may have the greatest benefit, specifically those aged ≥ 75 years and those with a history of hypertension.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

References

1. Koc F, Ozdemir K, Kaya MG, Dogdu O, Vatankulu MA, Ayhan S, et al. Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS – a multicenter prospective controlled trial. Int J Cardiol 2012; 155: 418–23.
2. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. N Engl J Med 2006; 354: 379–86.
3. Mehran R, Caixeta A. N-acetylcysteine in preventing contrast-induced nephropathy. To give, or not to give: that is the question. Rev Esp Cardiol 2010; 63: 9–11.
4. Briguori C, Quintavalle C, De Micco F, Condorelli G. Nephrotoxicity of contrast media and protective effects of acetylcysteine. Arch Toxicol 2011; 85: 165–73.
5. Tepel M, Van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000; 343: 180–4.
6. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331: 1416–20.
7. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004; 291: 2328–34.
8. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). Circulation 2011; 124: 1250–9.
9. Birck R, Krzossok S, Markowetz F, Schnulle P, Van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet 2003; 362: 598–603.
10. Alonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ. Prevention of radiocontrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. Am J Kidney Dis 2004; 43: 1–9.
11. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008; 148: 284–94.
12. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Section 4: contrast-induced AKI. KDIGO clinical practice guideline for acute kidney injury: a report from the International Society of Nephrology. Kidney Int Suppl 2012; 2: 69–88.
13. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011; 124: e574–651.
14. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.
15. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ, ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005; 293: 572–80.
16. Kay J, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA 2003; 289: 553–8.
17. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, et al. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med 2006; 354: 2773–82.