N-acetylcysteine for the Prevention of Contrast-induced Nephropathy in the Emergency Department

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Abstract

Objective To evaluate the use of N-acetylcysteine (NAC), a potent antioxidant, to prevent contrast-induced nephropathy (CIN).

Methods We prospectively studied 209 patients (106 in the NAC group and 103 in the control group) who received contrast-enhanced computed tomography (CECT) in the emergency department (ED). The NAC group received intravenous NAC (600 mg) before CECT imaging to prevent CIN. Both the NAC and control groups were treated using a standardized hydration strategy, where clinically feasible.

Results The patients’ mean age was 79.6±9.8 years. The prevalence of hypertension, diabetes, and chronic kidney disease (CKD) were 63.2%, 27.3%, and 21.5%, respectively. The baseline clinical characteristics were similar between the two groups except for their body weight (p=0.011), amount of contrast material administered (p=0.049) and prevalence of CKD (p=0.002). The incidence of CIN was 7.5% in the NAC group and 14.6% in the control group. The adjusted odds ratio was 0.305 (95% confidence interval: 0.097 to 0.960, p=0.042). All-cause mortality was 7.5% in the NAC group and 12.6% in the control group, which was not significantly different. Temporary hemodialysis was required in 0% of subjects in the NAC group and 1.0% in the control group, which was not a statistically significant difference.

Conclusion A single dose of NAC before CECT imaging can prevent CIN in an ED setting. However, it does not improve the mortality rate or the need for dialysis.

Key words: N-acetylcysteine, contrast media, nephropathy, prevention, computed tomography


Introduction

Over the past several decades, there has been a dramatic growth worldwide in the use of iodinated contrast-enhanced imaging. While contrast-enhanced procedures are safe in the majority of cases, serious complications can occur in some patients. One of the potentially serious complications associated with iodinated contrast use is contrast-induced nephropathy (CIN), a condition that is often transient. However, in some cases, transient dialysis may be required, especially in high-risk patients (1, 2).

The optimum strategy to prevent CIN remains unclear. The available evidence, which is based largely on small- to medium-sized trials, supports the use of hydration, bicarbonate, and low volumes of iso- or low-osmolar contrast media (CM) in patients at risk. N-acetylcysteine (NAC) or ascorbic acid may also be of value in high-risk patients (3).

The generation of reactive oxygen species has been considered an important pathophysiological cause of CIN (4). NAC is a potent antioxidant that scavenges a wide variety of oxygen-derived free radicals. NAC may prevent CIN by halting direct oxidative tissue damage and by improving renal hemodynamics (5, 6).
We hypothesized that NAC may be beneficial in the prevention of CIN. To our knowledge, there have been few studies focusing on the prevention of CIN in patients undergoing CECT scans in the emergency department (ED). Our aim was to use NAC, a potent antioxidant, to prevent CIN and further reduce morbidity and mortality in patients who received CECT in the ED.

**Materials and Methods**

Our study protocol was approved by our institutional ethics review board and written informed consent was obtained from all participants.

We conducted a prospective clinical trial on all adult patients who received abdominal or chest contrast-enhanced computed tomography (CECT) from November 2009 to April 2010, in an ED of a medical teaching center in northern Taiwan. Our center accommodates approximately 80,000 ED visits annually. We excluded those patients who underwent long-term hemodialysis or peritoneal dialysis, received another dose of contrast medium within 72 hours, refused to sign consent forms, or had a known allergy to N-acetylcysteine (NAC). All eligible patients were evaluated by the study researchers. If the patients met the inclusion criteria, they were invited by study physicians to participate in our study. Patients from the registered database from the CT room in the ED were first matched to our NAC group by age and their pre-contrast serum creatinine concentration. Then, an independent researcher (MK Huang) used computer-generated random numbers to acquire controls from matching patients.

We intravenously administered 600 mg of NAC in 0.9% sodium chloride (3 mL/kg) for 60 minutes prior to the start of the contrast injection. The control group was treated using the standardized hydration strategy, i.e., 3 mL/kg/h of 0.9% sodium chloride, for 60 minutes before CECT, if clinically feasible (7). In patients with congestive pulmonary edema, the rates of fluid loading were decreased to half (i.e., 1.5 mL/kg) in both groups. The infusion of 0.9% sodium chloride was continued at a rate of 1 mL/kg/h during, and for 6 hours after, CECT. The infusion rates were decreased to 0.5 mL/kg/h in patients with clinical evidence of congestive heart failure or pulmonary congestion. Adequate fluid resuscitation was not prohibited in patients with low blood pressure.

There are two major considerations when using intravenous NAC in the ED. First, these patients require emergency imaging procedures, in whom preventive therapy with oral NAC cannot be given the day before the procedure. Second, some of the patients demonstrated acute abdomen and were therefore ordered to be “nil per os”.

CECT was performed using one of three low-osmolar nonionic contrast media, including Iohexol (Omnipaque 350 mgI/mL, GE healthcare, Co. Cork, Ireland), Iobitridol (Xenetix 350 mgI/mL; Guerbet, Aulnay-sous-Bois, France), or Iopromide (Ultravisit 370 mgI/mL; Bayer Schering Pharma AG, Berlin, Germany).

**Definitions and endpoints**

The baseline serum creatinine concentration (SCr) was defined as the stable SCr at one year prior to the index CECT examination. The pre-contrast SCr and post-contrast SCr were obtained before, and 48 to 72 hours after, the index CECT examination during the same ED visit. The ΔSCr was the difference between the post-contrast SCr and pre-contrast SCr.

The creatinine clearance (CrCl) was estimated using the Cockcroft-Gault formula (8), where: 

$$
{	ext{CrCl}} = \left[ {\frac{{[140 - \text{age}] \times \text{weight (kg)/SCr (mg/dL)} \times 72}}{1.73}} \right] \text{mL/min}
$$

with adjustment for female gender (CrCl female = CrCl × 0.85). To estimate the glomerular filtration rate (eGFR), we used the simplified Modification of Diet in Renal Disease (MDRD) formula (9):

$$
\text{eGFR} (\text{mL/min/1.73 m}^2) = 186 \times (\text{creatinine, mg/dL})^{1.154} \times (\text{age, years})^{-0.203} \times (0.742 \text{in women}).
$$

Chronic kidney disease (CKD) was defined either by history or when the baseline SCr was >1.5 mg/dL. Renal insufficiency (RI) was defined as a pre-contrast SCr >1.5 mg/dL or pre-contrast eGFR <60 mL/min/1.73 m². Comorbidities were scaled according to the Charlson Comorbidity Index (10). Shock was defined by the requirement of vasopressors despite adequate fluid resuscitation. CIN05 was defined as an increase in the SCr ≥0.5 mg/dL within 48 to 72 hours after CECT imaging. CINor was defined as an increase in the SCr ≥0.5 mg/dL or by 25% within 48 to 72 hours after CECT imaging (11-13).

The primary endpoint of the study was the occurrence of CIN, defined as CIN05 or CINor. The secondary endpoints were the need for temporary or permanent renal replacement therapy and the all-cause in-hospital mortality.

**Statistic analysis**

Based on previous findings, a sample size of 106 patients in each group was considered to be sufficient to detect a difference of 12% between the groups in the rate of CIN, with 80% power and a 5% significance level (14, 15). This 12% difference represents the difference between a 17% CIN rate in the control group and a 5% rate in the NAC group. This number was increased to 117 per group to allow for a predicted drop-out rate of approximately 10%.

The continuous data were expressed as the means ± SD and the categorical data were expressed as the numbers and percentages. A statistical analysis was performed using independent t-tests for continuous variables, the chi-square test or Fisher’s exact test for univariate categorical variables, and binary logistic regression for the multivariate analysis. A two tailed p<0.05 was considered to be statistically significant.

The sample size estimation was performed with the SigmaStat software program for Windows, version 1.0 (Jandel Corp, San Rafael, California, USA). The statistical data were analyzed with the SPSS software version 16.0 (SPSS Inc, Chicago, Illinois, USA).
2,233 patients underwent CT scanning during study period
804 patients (36%) screened during the work shift of study physicians
732 patients (91%) met inclusion criteria
120 patients allocated to NAC group
2 did not received intravenous CM
12 did not have follow-up SCr
120 matched controls allocated to control group
3 did not received intravenous CM
14 did not have follow-up SCr
106 patients were evaluable
103 patients were evaluable

**Figure 1.** A flow diagram of patient enrollment.

**Results**

**Patients**

Of the 120 patients enrolled in the NAC group, two patients did not receive intravenous contrast media and 12 patients were lost to the follow-up because of immediate ED discharge after CECT imaging and failure to have subsequent blood sampling. Therefore, 106 patients (88% of the enrollees) were evaluable for assessment of outcomes in the NAC group. Of the 120 matched patients enrolled in the control group, three patients did not receive intravenous contrast media and 14 patients were lost to follow-up because of immediate ED discharge after CECT imaging. Thus, only 103 patients (86% of enrollees) were evaluable for the assessment of outcomes in the control group (Fig. 1).

The mean age of our study patients was 79.6±9.8 years. The mean pre-contrast SCr was 1.60±0.60 mg/dL, and the mean eGFR was 49.7±28.8 mL/min/1.73 m². The prevalence of hypertension, diabetes, and CKD was 63.2%, 27.3%, and 21.5%, respectively. Details of the patients’ baseline clinical, pharmacological, and laboratory characteristics are presented in Table 1.

There were no significant differences between the NAC and control groups with regard to most baseline characteristics, except for body weight (p=0.011), the amount of contrast material administered (p=0.049), and the presence of CKD (p=0.002).

**Primary endpoint**

The incidence of CIN05 was not significantly different between the NAC and control groups (7.5% vs. 14.6%, respectively, in a univariate analysis with an odds ratio [OR]: 0.479, 95% confidence interval [CI]: 0.194-1.184; p>0.05). CINor was also not significantly different between the NAC and control groups (11.3% vs. 19.4%, respectively, according to a univariate analysis with OR: 0.530, 95% CI: 0.244-1.149; p>0.05).

After adjusting for body weight, the amount of contrast material administered and the presence of CKD, we found that the use of NAC significantly prevented CIN for both definitions (CIN05, adjusted OR: 0.305, 95% CI: 0.097-0.960; CINor, adjusted OR: 0.346, 95% CI: 0.131-0.909; Table 2). Even after adjustment for age, gender and the status of major systemic disease, NAC administration also significantly prevented CIN for both definitions with a similar odds ratio. In patients with renal insufficiency, the subgroup analyses demonstrated borderline CIN protection in the NAC group using the CINor definition (Fig. 2).

**Figure 2.** The results of the subgroup analyses. RI: renal insufficiency, see text for details about the definition. RI (-) means no renal insufficiency, RI (+) means renal insufficiency.

* Adjusted p value = 0.056
Table 1. Baseline Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>NAC n = 106</th>
<th>Control n = 103</th>
<th>Overall n = 209</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>79.7 (8.5)</td>
<td>79.3 (11.1)</td>
<td>79.6 (9.8)</td>
<td>0.772</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>28 (26.4%)</td>
<td>25 (24.3%)</td>
<td>31 (29.2%)</td>
<td>0.107</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>62.9 (12.8)</td>
<td>58.5 (11.3)</td>
<td>60.8 (12.1)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Contrast, mL</td>
<td>91.1 (10.0)</td>
<td>88.1 (10.0)</td>
<td>89.3 (10.1)</td>
<td>0.049*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>70 (66.0%)</td>
<td>62 (60.2%)</td>
<td>132 (63.2%)</td>
<td>0.381</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>31 (29.2%)</td>
<td>26 (25.2%)</td>
<td>57 (27.3%)</td>
<td>0.516</td>
</tr>
<tr>
<td>Chronic Kidney Disease, n (%)</td>
<td>32 (30.2%)</td>
<td>13 (12.6%)</td>
<td>45 (21.5%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Renal insufficiency, n (%)</td>
<td>15 (14.2%)</td>
<td>15 (14.6%)</td>
<td>30 (14.4%)</td>
<td>0.932</td>
</tr>
<tr>
<td>Cerebral vascular accident, n (%)</td>
<td>19 (17.9%)</td>
<td>23 (22.3%)</td>
<td>42 (20.1%)</td>
<td>0.472</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>18 (17.0%)</td>
<td>12 (11.7%)</td>
<td>30 (14.4%)</td>
<td>0.272</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3.12 (2.62)</td>
<td>2.56 (2.27)</td>
<td>2.85 (2.46)</td>
<td>0.100</td>
</tr>
<tr>
<td>NSAID, n (%)</td>
<td>9 (8.5%)</td>
<td>7 (6.8%)</td>
<td>16 (7.7%)</td>
<td>0.645</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>20 (18.9%)</td>
<td>25 (24.3%)</td>
<td>45 (21.5%)</td>
<td>0.142</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>19 (17.9%)</td>
<td>22 (21.4%)</td>
<td>41 (19.6%)</td>
<td>0.532</td>
</tr>
<tr>
<td>Aminoglycoside, n (%)</td>
<td>0 (0%)</td>
<td>1 (1.0%)</td>
<td>0 (0.5%)</td>
<td>0.493</td>
</tr>
<tr>
<td>Shock, n (%)</td>
<td>10 (9.4%)</td>
<td>12 (11.7%)</td>
<td>22 (10.5%)</td>
<td>0.602</td>
</tr>
</tbody>
</table>

* p < 0.05


Values are mean (SD) or number (percentage).

Table 2. Primary and Secondary End-points in NAC and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>NAC n = 106</th>
<th>Control n = 103</th>
<th>Unadjusted OR, 95% CI</th>
<th>p value</th>
<th>Adjusted* OR, 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN05*</td>
<td>7.5%</td>
<td>14.6%</td>
<td>0.479</td>
<td>0.305</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.194 – 1.184</td>
<td>0.097 – 960</td>
<td>0.346</td>
<td>0.131 – 0.909</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>CINor*</td>
<td>11.3%</td>
<td>19.4%</td>
<td>0.244 – 1.149</td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.565</td>
<td>0.489</td>
<td>0.154 – 1.550</td>
<td>0.224</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>7.5%</td>
<td>12.6%</td>
<td>0.224 – 1.427</td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.223</td>
<td>0.565</td>
<td>0.154 – 1.550</td>
<td>0.224</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CIN05 was defined as a rise in SCr ≥ 0.5mg/dL within 48 to 72 hours after CECT imaging. CINor was defined as a rise in SCr ≥ 0.5mg/dL or 25% within 48 to 72 hours after CECT imaging.

Discussion

No differences were observed between groups regarding the incidence of all-cause mortality (7.5% in the NAC group vs. 12.6% in the control group; OR: 0.565, 95% CI: 0.224-1.427). After adjustment for unbalanced baseline variables (body weight, amount of contrast material administered, and presence of CKD), there was still no difference between the groups regarding the incidence of all-cause mortality (OR: 0.489, 95% CI: 0.154-1.550; Table 2). The incidence of temporary renal replacement therapy was 0% in the NAC group and 1.0% in the control group. The incidence of permanent renal replacement therapy was 0% in both groups.

Because of low event rates, we did not perform any statistical analyses for these endpoints.

Discussion

We found that a single 600 mg intravenous dose of NAC administered one hour prior to contrast administration significantly reduced the risk of CIN in patients in the ED setting. A nationwide survey in the US showed that CT use increased by 330% between 1996 and 2007 in the ED (16). Some reports have indicated that CT use in the ED may be increasing more sharply relative to its use in other clinical settings. Factors responsible for this trend include a need for...
rapid, accurate diagnosis, a general trend toward less invasive testing, an increasing concern about malpractice litigation, and an increasing public awareness of (and often desire for) CT scanning capabilities (17-20).

CIN, the development of acute renal failure after the administration of contrast in the absence of other identifiable causes, is the third leading cause of new-onset renal failure in hospitalized patients (11). Retrospective studies have demonstrated an association between CIN and a prolonged hospital stay, higher rates of in-hospital clinical complications, increased health care costs, and increased in-hospital and 1-year mortality rates (1, 21-23).

Several risk factors for CIN have been reported, including CKD, diabetes mellitus, congestive heart failure, advanced age, hemodynamic instability, anemia, use of an intra-aortic balloon pump, nephrotoxic drug use, as well as the type and dose of contrast media used (24, 25). Metabolic syndrome, hyperuricemia, and prediabetes were recently identified as additional risk factors (26).

However, most studies that have identified these risk factors were performed in patients undergoing coronary angiography or percutaneous coronary intervention (PCI) using a higher dose of CM than those administered during CECT scans in the ED. In addition, the clinical characteristics of acutely ill patients seen in the ED may differ significantly from those of patients undergoing coronary angiography, since ED patients often have more complicated risk factors and present in a more debilitated clinical condition.

Of particular significance was our finding that the incidence of CIN is probably higher than might be predicted for the ED population. The incidence of CIN observed in our control group (CIN05 14.6%, CINor 19.4%) was over three times the rate of CIN reported in the literature after coronary angiography (4%) in low-risk populations and is within the range reported for moderate- to high-risk populations (27). The incidence of CIN (using our CINor definition, see the above text) was 6.5% following nonemergency CT among outpatients with mild baseline kidney disease, and 11% among low risk and relatively young ED patients undergoing CT (28-30). The incidence of CIN observed in our NAC group (CIN05 7.5%, CINor 11.3%) was also four times greater than the 2.5% rate of CIN (use CINor definition, see above text) observed after CECT in NAC pre-treated outpatients (31).

Our ED patients suffered from various risk factors for CIN, including advanced age (79.6±9.8 years) and poor renal function (pre-contrast Scr 1.60±0.60 mg/dL and eGFR 49.7±28.8 mL/min/1.73 m²). In spite of a broad range of presenting complaints, including acute or even critical illnesses, all patients made the practical decision to use preventive measures against CIN.

Careful pre-procedural stratification has been recommended. The risk score proposed by Mehran is useful for performing an individual patient risk assessment prior to coronary angioplasty or PCI (24). However, its application to stratified ED patients was not appropriate because of the differences in the clinical condition of ED patients compared to coronary angioplasty or PCI patients. For example, patients who received coronary angioplasty or PCI were elective patients who were relatively stable. In the ED setting, most patients were acutely ill with unstable conditions that limited the selection and use of preventive measures for CIN.

Despite the use of low-osmolarity CM and prophylactic hydration, impairment of renal function after CM administration continues to be a significant clinical problem. Furthermore, it is often not possible to delay CECT until adequate hydration has been achieved in the emergency setting. Additionally, the resulting volume load of approximately 2 L/d is not without risk, especially for patients in the time-sensitive ED who have a poor left ventricular function, adult respiratory distress syndrome, or decompensated cirrhosis.

In patients undergoing CECT, additional efforts should be made to protect them from additional injury, and the use of a single dose IV NAC, although not proven, has been suggested to be protective in the ED setting. According to our results, use of a single dose NAC will significantly reduce the risk of the development of CIN, but does not reduce the risk of all-cause in-hospital mortality.

Although creatinine is routinely used to characterize renal function, many studies and guidelines recommend using the eGFR since it was found to be more accurate. In a recent study, the serum creatinine, but not eGFR, was found to be predictive for long-term mortality, with a threshold of 0.5 mg/dL or more indicating a worse prognosis (32). For most clinical applications, the SCr is easier to measure and rapidly collect in the ED setting.

It has been pointed out that the advantages provided by NAC administration might be related to a decrease in the SCr, reflecting either an increase in creatinine excretion or a decrease in creatinine production (33). Since the subjects in that study were healthy volunteers and the SCr difference after oral NAC use was only 0.03 mg/dL, this small difference may not have had clinical significance and may not apply to acutely ill patients. On the other hand, Izzedine and his colleague reported that a therapeutic dose of NAC did not interfere with serum creatinine assays (34), therefore, large-scale studies should be performed in the future to determine the impact of oral NAC use.

Study limitations

Our study had several limitations. First, this study was performed in a single ED of an academic, urban medical center, and the results may vary in other settings. The study design was a prospective matched control trial, not an ideal randomized control trial. Although controls that matched our NAC group by age and pre-contrast Scr levels were randomly acquired from a registered database, there were unbalanced baseline clinical parameters and, potentially, an unknown selection bias. In the ED, it is not possible to accurately evaluate renal function, such as can be done by examining the 24 hours creatinine clearance before CT scanning.
Therefore, we used SCR and eGFR as surrogates for risk stratification. In addition, our case numbers were not large enough to analyze the adverse event rates for either short-term or long-term renal replacement therapy. Finally, further large scale randomized controlled trials in patients undergoing CECT in the ED are required to fully elucidate the effect of NAC in preventing CIN and possibly even preventing the need for renal replacement therapy or death.

In conclusion, we found that a single dose of NAC before CECT imaging can prevent CIN, but cannot prevent the risk of mortality and short-term or long-term renal replacement therapy in the ED setting.

The authors state that they have no Conflict of Interest (COI).

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References