# *N*-acetylcysteine for radiocontrast-induced nephropathy: Potential role in the emergency department?

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**ABSTRACT**

**Objective:** To systematically review the efficacy and safety of *N*-acetylcysteine (NAC) for the prevention of radiocontrast-induced nephropathy (RIN), and to discuss its potential role in the emergency department.

**Methodology:** We conducted a search of MEDLINE (from 1966 to December 2003), PubMed (1966 to December 2003) and EMBASE (1988 to December 2003) for English-language, prospective, randomized, controlled trials in humans using the search terms *N*-acetylcysteine, acetylcysteine, radiopharmaceuticals, contrast media, and kidney failure (acute).

**Results:** Five trials support and 4 trials refute the hypothesis that NAC helps prevent RIN. In 7 of 9 trials, oral NAC was administered twice daily for 2 days, on the day before and on the day of the radiocontrast study — a regime not feasible for emergent situations. More recent trials suggest that adequate hydration and lower volumes of radiocontrast, rather than NAC, are more effective ways to prevent RIN.

**Conclusion:** Although further study may be indicated, current evidence does not suggest that NAC has a role in the emergency prevention of RIN.

**Key words:** *N*-acetylcysteine; radiocontrast; emergency; renal failure; nephropathy

**RÉSUMÉ**

**Objectif :** Procéder à une revue systématique de l'efficacité et la sécurité de la *N*-acétylcystéine pour la prévention de la néphropathie induite par les produits de contraste et discuter de son rôle potentiel au département d'urgence.

**Méthodologie :** Nous avons procédé à une recherche de MEDLINE (de 1966 à décembre 2003), PubMed (1966 à décembre 2003) et EMBASE (1988 à décembre 2003) pour des essais en langue anglaise prospectifs, randomisés et contrôlés chez des humains en utilisant les termes de recherche suivants : *N*-acétylcyctéine, acétylcystéine, produits pharmaco-radioactifs, produits de contraste et insuffisance rénale (aiguë).

**Résultats :** Cinq essais appuient et quatre essais réfutent l'hypothèse selon laquelle la *N*-acétylcystéine prévient la néphropathie induite par les produits de contraste. Parmi sept des neuf essais, la *N*-acétylcystéine fut administrée par voie orale deux fois par jour pendant deux jours, soir le jour avant et le jour même de l'étude avec produit de contraste, un régime irréalisable en situation d'urgence. Des essais plus récents ont évoqué qu'une hydratation adéquate et des volumes moins

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Received: Jan. 18, 2004; final submission: Apr. 13, 2004; accepted: Apr. 20, 2004.

*This article has been peer reviewed.*

*Can J Emerg Med* 2004;6(4):253-8

élevés de produit de contraste, plutôt que la *N*-acétylcystéine, constituaient un moyen plus efficace de prévenir la néphropathie induite par les produits de contraste.
**Conclusion :** Bien que des études plus poussées soient indiquées, les preuves actuelles ne corroborent pas l'utilité de la *N*-acétylcystéine dans la prévention de la néphropathie induite par les produits de contraste en situation d'urgence.

## Introduction

Many patients in the emergency department (ED) require radiocontrast diagnostic imaging. Unfortunately, radiocontrast administration is the third leading cause of hospital-acquired acute renal failure, which is associated with high morbidity and mortality.[1–4] Radiocontrast-induced nephropathy (RIN) is defined as an abrupt deterioration in renal function in the absence of other identifiable causes.[4] The clinical course of RIN can range from transient elevations in serum creatinine (SCr) to permanent renal failure requiring dialysis.[5] Factors contributing to RIN include renal medullary hypoxia through intra-renal vasoconstriction and increased distal delivery of solutes, as well as direct tubular injury mediated by reactive oxygen species or tubular obstruction.[4,5]

Pre-existing renal insufficiency is considered a major risk factor for RIN. The probability of RIN requiring dialysis increases from 2% to 48% as the precontrast creatinine clearance decreases from 30 to 10 mL/min.[6] Other risk factors include diabetes mellitus, intravascular volume depletion, older age, increased dose of contrast material, use of ionic and higher osmotic radiocontrast agents, concurrent use of nephrotoxic drugs, congestive heart failure (New York Heart Association [NYHA] Class III and IV), liver cirrhosis and multiple myeloma.[4,5,7] The exact incidence of RIN for patients requiring ED contrast studies is unknown. However, ED patients may be at higher risk because proper pre-contrast risk assessments are not always obtained and because the urgent need for imaging may preclude other prophylactic measures — notably hydration. For these patients any prophylactic intervention that may reduce the development of RIN must be considered.

*N*-acetylcysteine (NAC) has been used for years to treat acute acetaminophen poisoning and a variety of pulmonary diseases.[8] Emerging data suggest that NAC prevents ischemia-reperfusion syndromes in vital organs, and may also protect tissues by scavenging circulating free radicals.[8] NAC is also a potent vasodilator that enhances renal perfusion by increasing the expression of nitric oxide synthase and thus nitric oxide.[8] Finally, NAC may exert its antioxidant effect indirectly by facilitating glutathione biosynthesis.[4] Recently, the drug has generated considerable interest as a prophylactic agent for RIN . The purpose of this paper is to systematically review the efficacy and safety of NAC for the prevention of RIN, and to discuss its role in the ED.

## Methods

### *Data source*

A systematic search of MEDLINE (1966 to December 2003), PubMed (1966 to December 2003), and EMBASE (1988 to December 2003) databases was conducted for English-language, prospective, randomized, controlled trials describing the prophylactic use of NAC prior to radiocontrast administration in humans. The following search terms were used: *N*-acetylcysteine; acetylcysteine; radiopharmaceuticals; contrast media; and kidney failure (acute). Additional published reports were identified through a manual search of reference lists in retrieved articles and in review articles.

### *Study selection*

Both authors independently evaluated the title and abstract of all identified citations for inclusion. Only full-text, prospective, randomized, comparative evaluations of NAC for the prevention of RIN were included. Abstracts, retrospective studies, non-randomized prospective trials and animal studies were excluded. Where uncertainty remained regarding eligibility for inclusion, full text was reviewed.

### *Data extraction*

Data elements for all trials were evaluated independently by both authors. Data elements extracted included study design, number of subjects involved, patient population and risk factors for RIN, radiocontrast agent used, radiocontrast procedure performed, NAC regimen (dose, route and duration), co-interventions and clinical outcomes (efficacy and safety). For the primary efficacy endpoint of RIN, the definition specified in each individual study was reported.

## Results

Nine trials involving 1019 patients met inclusion criteria. Five trials demonstrated that prophylactic NAC administration prevented RIN,[9–13] and 4 suggested it does not.[14–17]



https://doi.org/10.1017/S1481803500009210 Published online by Cambridge University Press

### *Trials demonstrating benefit*

Tepel and colleagues[9] performed a prospective, randomized, placebo-controlled trial in 83 adults with chronic renal insufficiency who required radiocontrast prior to computed tomography. Patients received either NAC 600 mg PO twice daily or placebo for 2 days (on the day before and on the day of radiocontrast administration). Contrast-induced reduction in renal function, defined as an increase in SCr concentration of at least 44 mmol/L at 48 hours after radiocontrast administration, was observed in 1 of 41 patients (2%) in the NAC group and 9 of 42 patients (21%) in the control group ($p = 0.01$, relative risk [RR] = 0.1, 95% confidence interval [CI] 0.02–0.9). The absolute 48-hour change in SCr was also significantly different between groups ($p < 0.001$).

Diaz-Sandoval and coworkers[10] performed a randomized, double-blind, placebo-controlled trial in 54 patients with chronic renal insufficiency undergoing elective cardiac catheterization. Patients received either NAC 600 mg PO twice daily or placebo for 2 days. One dose was given before and 3 doses after catheterization. Contrast-induced reduction in renal function, defined as an increase in SCr concentration of at least 44 mmol/L or a greater than 25% increase in SCr above baseline, at 48 hours after catheterization, was observed in 2 of 25 patients (8%) in the NAC group and 13 of 29 patients (45%) in the control group ($p = 0.005$, RR = 0.21, 95% CI 0.06–0.8). The absolute change in SCr at 48 hours following contrast was significantly greater in the control compared to the NAC group ($p < 0.0001$).

Shyu and associates[11] evaluated 121 adults with chronic renal insufficiency undergoing elective diagnostic cardiac angiography and percutaneous coronary intervention (PCI). Patients were randomized to receive either NAC 400 mg PO twice daily for 2 days (on the day before and on the day of coronary angiography) or matching placebo. Contrast-induced renal dysfunction, defined as an increase in SCr concentration of at least 44 mmol/L at 48 hours after radiocontrast administration, was observed in 2 of 60 patients (3.3%) in the NAC group and 15 of 61 patients (25%) in the control group ($p < 0.001$, RR = 0.13, 95% CI 0.08–0.20). Lower mean SCr concentrations in the patients who received NAC were sustained out to 7 days after radiocontrast administration. The absolute change in SCr 48 hours after contrast administration was significantly greater in the control compared to the NAC group ($p < 0.001$).

Kay and colleagues[12] performed a prospective, randomized, double-blind, placebo-controlled trial in 200 patients with chronic renal insufficiency requiring PCI. Patients received either NAC 600 mg PO twice daily for 2 days (on the day before and on the day of radiocontrast administration, 3 doses to be given before and 1 dose after catheterization) or matching placebo. Contrast-induced reduction in renal function was defined as an increase in SCr concentration >25% above baseline at 48 hours after radiocontrast administration, was seen in 4 of 102 patients (4%) in the NAC group and 12 of 98 patients (12%) in the control group ($p = 0.03$). Differences in changes from baseline between NAC and control groups were not significant at day 7. When 24-hour creatinine clearance was examined, the increase in the control group was only significant compared to baseline at day 7 ($p < 0.001$). NAC appeared to be of greater benefit among patients who had diabetes mellitus ($p = 0.001$) and those who received >100 mL of contrast media ($p < 0.001$).

Baker and coworkers[13] performed a prospective, randomized, multicentre trial using NAC intravenously (IV) in a rapid protocol in patients undergoing coronary angiography (RAPPID trial). Eighty adults with stable chronic renal insufficiency received either IV NAC 150 mg/kg in 500 mL of 0.9% saline over 30 minutes immediately before contrast administration, followed by 50 mg/kg in 500 mL of 0.9% saline over the subsequent 4 hours, or 0.9% saline at a rate of 1 mL/kg/h for 12 hours pre- and post-procedure. Contrast-induced reduction in renal function, defined as an increase in SCr concentration of at least 25% above baseline at either 48 or 96 hours after radiocontrast administration, was observed in 2 of 41 patients (4.9%) in the NAC group and 8 of 39 patients (20.5%) in the control group ($p = 0.045$, RR = 0.28, 95% CI 0.08–0.98). The change in SCr was significantly different in the control compared to the NAC group at both 48 hours ($p = 0.044$) and 96 hours ($p = 0.008$).

### *Trials demonstrating no benefit*

Briguori and associates[14] evaluated 183 patients with impaired renal function undergoing PCI. Study subjects were randomized to receive NAC 600 mg PO twice daily or saline hydration alone for 2 days (on the day before and on the day of radiocontrast administration). Contrast-induced reduction in renal function, defined as an increase in SCr concentration at least 25% above baseline at 48 hours, or the need for dialysis in the first 5 days after the intervention, was seen in 6 of 92 patients (6.5%) in the NAC group and 10 of 91 patients (11%) in the control group ($p = 0.22$). Renal failure requiring temporary dialysis occurred in only 1 patient in the control group (1.1%). No statistically significant changes in SCr concentrations from baseline and the treatment strategy were observed. However, a significant correlation was found between the absolute change in SCr and the amount of contrast in the



https://doi.org/10.1017/S1481803500009210 Published online by Cambridge University Press

NAC group ($p < 0.001$). A threshold value of contrast media volume ≥140 mL predicted the occurrence of RIN (sensitivity 89%, specificity 55%). In the subgroup with low volume contrast dose (<140 mL), renal function deterioration did not occur in any patients receiving NAC compared to 5 of 60 patients (8.5%) in the control group ($p = 0.02$, odds ratio [OR] = 0.44, 95% CI 0.35–0.54). In the subgroup with high contrast dose (≥140 mL), no differences were seen.

Allaqaband and colleagues[15] performed a randomized, comparative, 3-arm trial in 123 patients scheduled for coronary angiography (67%), angiography with PCI (27%) or peripheral angioplasty (6%). Patients received either (i) NAC 600 mg PO twice daily for 2 days (on the day before and on the day of radiocontrast administration) plus saline hydration; (ii) fenoldopam 0.1 mg/kg/min IV starting 4 hours before the procedure and continued for 4 hours after plus saline hydration; or (iii) saline hydration alone. Contrast-induced reduction in renal function, defined as an increase in SCr concentration of at least 44 mmol/L (0.5 mg/dL) within 48 hours of contrast exposure, occurred in 8 of 45 patients (17.7%) in the NAC group, 6 of 38 patients (15.7%) in the fenoldopam group, and 6 of 40 patients (15.3%) in the saline-only group ($p$ = NS). There were no differences in absolute changes in SCr at 24 or 48 hours after administration of radiocontrast.

Durham and coworkers[16] evaluated 79 patients undergoing PCI. Study subjects were randomized to receive NAC 1200 mg PO or placebo × 2 doses (1 hour prior to radiocontrast, and 3 hours after cardiac catheterization). Contrast-induced reduction in renal function was defined as an increase in SCr concentration of at least 44 mmol/L within 48 hours of contrast exposure. There was no significant difference in this endpoint among the groups (26.3% NAC v. 22.0% control). Among the patients with diabetes mellitus, there was a non-significant trend toward an increased risk of renal failure in patients treated with NAC (42.1% NAC v. 27.8% control, $p = 0.09$). Through multivariate analysis, diabetes mellitus and elevated baseline SCr remained independent predictors of acute renal failure risk.

Oldemeyer and associates[17] studied 96 patients with stable chronic renal insufficiency who were undergoing elective coronary angiography. Subjects were randomized to receive NAC 1500 mg PO twice daily or placebo × 4 doses (the evening before and the day of the coronary angiography). Contrast-induced nephropathy was defined as an increase in SCr concentration of ≥44 mmol/L, or ≥25% compared to baseline, within 24 or 48 hours of contrast exposure. There was no significant difference in this endpoint among the groups (8% NAC v. 6% control, $p = 0.74$).

### *Adverse effects*

There were variable reports of adverse effects throughout the trials. In the trial by Tepel and colleagues,[9] transient gastrointestinal discomfort (7% NAC v. 12% control) and dizziness (10% NAC v. 7% control) were the only reported adverse effects. Kay and colleagues[12] reported that 1 subject receiving placebo discontinued the trial because of nausea. Oldemeyer and associates[17] reported adverse effects in 16% of patients in the NAC group. These were mostly gastrointestinal symptoms, including nausea, stomach discomfort, diarrhea and constipation, although 1 patient reported a headache, and another patient experienced chest tightness. Five trials did not report adverse effects.[10,11,14–16]

In the only trial using IV NAC, adverse events occurred in 10 of 80 patients (12.5%). Pulmonary edema was seen in 2 patients (5%) from each group. Itching, flushing or transient rash was reported in 6 patients (14.6%) in the NAC group after the 30-minute infusion. Symptoms resolved spontaneously after stopping the infusion in all 6 patients. Three of these patients declined the 4-hour infusion after experiencing this adverse reaction.[13]

## Discussion

Radiocontrast materials may cause nephrotoxicity, and emergency physicians should assess the risk of RIN prior to giving these agents. Unfortunately, patients often require urgent contrast imaging regardless of risk. The appeal of NAC in these situations is that it is relatively nontoxic and emergency physicians are familiar with its use.

Five randomized, controlled trials support the hypothesis that NAC is renoprotective,[9–11,13] and 4 others do not.[14–17] The reasons for this discrepancy are not entirely clear. The early trial of Tepel and colleagues,[9] which generated much initial interest in the use of NAC, differs from subsequent studies. Patients in this trial received small volumes of radiocontrast (75 mL),[9] and those in the other trials received much larger volumes (mean 77–238 mL).[10–18] In addition, the baseline SCr concentrations of patients in the trial by Tepel and colleagues (221 mmol/L) were generally higher than in any of the negative trials.[9–18] Since pre-existing renal insufficiency is a known risk factor for RIN, the positive results seen may be a reflection of benefits seen in higher-risk patients.

### *Applicability to the ED*

The studies described cannot necessarily be generalized to



https://doi.org/10.1017/S1481803500009210 Published online by Cambridge University Press

emergency medicine. Seven of these trials involved patients undergoing elective imaging and studied NAC administration 12–24 hours before radiocontrast administration,[9–12,14,15,17] and only 2 trials approximated emergency conditions.[13,16] The RAPPID study, which showed benefit in an emergency setting,[13] used intravenous NAC, 150 mg/kg over 30 minutes before contrast administration followed by 50 mg/kg over the next 4 hours (a regimen like that used for acetaminophen overdose). This more aggressive regimen appeared to reduce acute contrast-induced renal dysfunction but was associated with more adverse effects than reported in trials using lower-dose oral NAC. The investigators cautioned against the IV protocol in patients with impaired left ventricular function because the incidence of pulmonary edema was higher than expected in this study. Although higher-risk patients are more likely to benefit from NAC, pulmonary edema is a serious complication that may limit its use in this population. Hypersensitivity reactions, albeit manageable, were also observed in 15% of patients with the IV regimen.[13]

A trial evaluating acute NAC administration orally just prior to radiocontrast administration in patients undergoing emergency cardiac catheterizations failed to show a renoprotective benefit.[16] Durham and coworkers used a 1200-mg PO dose that was administered 1 hour prior to the procedure and then a second 1200-mg PO dose was repeated 3 hours after catheterization. These researchers justified this regimen based on the pharmacokinetic properties of NAC.

A recent meta-analysis included 7 of the 9 studies discussed in this systematic review and encompassed 805 patients,[19] but only 1 of the trials involved acute procedures done in an emergency setting.[9–12,14,15,17] Using a random-effects model, the authors concluded that NAC and hydration significantly reduced the relative risk of RIN by 56% (relative risk 0.44, 95% CI 0.22–0.88, $p = 0.02$) compared with peri-procedural hydration alone. Limitations of the meta-analysis include a documented publication bias as evidenced by an asymmetrical funnel plot. This may have lead to an over-estimation of the treatment effect. The authors also acknowledge that surrogate markers of renal function are utilized as the primary outcome for all included studies. Finally, the effects of the 2 most recent trials[13,17] on the results of the meta-analysis are unknown because their results were not available prior to publication of the meta-analysis.

A complicating factor for ED patients is that the urgent need for imaging may not allow sufficient time for adequate protective hydration. To illustrate, a recent study of patients requiring urgent cardiac catheterization used a hydration regimen of 0.45% saline at 75 mg/h. In this study,[16] the mean pre-procedure hydration volume was approximately 900 mL, suggesting the need for a 12-hour hydration period prior to "emergency" catheterization. This 12-hour time period, which is similar to standard hydration protocols, seems unrealistic in the ED setting.

### *The importance of pharmacokinetics*

NAC's elimination half-life is approximately 6.25 hours; therefore administration on the day prior to contrast exposure may not be effective.[18] Furthermore, a dose-ranging study of 200-, 600- or 1200-mg NAC in 10 healthy subjects found that pharmacokinetic parameters did not differ between a single 600-mg PO dose and repeated administration of 600 mg PO twice daily for 5 days.[20] This suggests that the clinical effects of NAC are not secondary to accumulation in plasma and that a shorter course of NAC may be as effective as the longer courses studied.

### *Study limitations*

The trials discussed had small sample sizes and studied heterogenous patient populations with varying comorbidities and degrees of renal insufficiency. The definition of RIN also varied among the trials, and most of the studies utilized SCr, an indirect marker of renal function, which was usually measured only out to 48 hours following contrast administration. Given that RIN typically peaks at 3–5 days and resolves at 7–10 days, a single creatinine measurement at 48 hours may only reflect transient increases that are clinically insignificant.[5] Long-term outcomes (beyond 7 days) were not studied in any trial. Moreover, investigators who attempted to determine the highest-risk patients through multivariate analyses did so using post-hoc methodologies on small groups of patients. Differences in NAC regimens, hydration regimens and choice of radiocontrast agent are also potential confounders.

## Conclusion

Studies of NAC prophylaxis for non-urgent radiocontrast procedures have produced conflicting results. More recent trials suggest that adequate hydration and lower volumes of radiocontrast may be more important methods of preventing RIN. Current evidence does not support the use of NAC for urgent radiologic investigations requiring contrast in the ED. A well designed prospective trial evaluating NAC just prior to radiocontrast administration in high-risk ED patients would help clarify the role of NAC in this setting.

**Competing interests:** None declared.

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