# *N*-acetylcysteine in the prevention of contrast agent-induced nephrotoxicity in patients undergoing computed tomography studies

*Hossein Khalili*[†], *Simin Dashti-Khavidaki, Hamed Tabifar, Nasrin Ahmadinejad & Farrokhlegha Ahmadi*

[†]*Author for correspondence*
*Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*
*Tel.: +98 912 297 9329*
*Fax: +98 216 646 1178*
*khalilih@sina.tums.ac.ir*

**Background:** Renal toxicity of contrast media remains an ever-present challenge. Contrast agent-induced nephrotoxicity (CIN) is defined as a serum creatinine rise of at least 25% from baseline, 48–72 h after contrast-agent infusion. It is suggested that prophylactic administration of *N*-acetylcysteine 600 mg orally twice daily for 2 days along with hydration prevents CIN, 48 h after contrast-agent administration in patients undergoing coronary or peripheral angiography. **Aims:** This study was designed to evaluate the efficacy of *N*-acetylcysteine 1200 mg once-daily oral administration on the day before and the day of imaging for the prevention of CIN during a 72 h follow-up of patients receiving contrast agents for abdominal and chest computed tomography (CT) scanning. **Methods:** A total of 70 patients with renal insufficiency (serum creatinine level ≥1.2 mg/dl) who referred to our institution for abdominal or chest CT scanning were randomly assigned to receive either only normal saline before contrast-agent administration (control group) or normal saline plus *N*-acetylcysteine 1200 mg single daily oral dose on the day before imaging and at the day of contrast-agent injection (*N*-acetylcysteine group). Both groups were comparable in terms of demographics, disease states, drug regimens, risk factors for developing CIN, type of imaging and type, volume or concentration of contrast agent used. **Results:** A total of 70 patients (35 per group) completed the study. The mean of serum creatinine concentrations were increased over 72 h follow-up in both groups; however, the change in serum creatinine level was greater in the control than the *N*-acetylcysteine group ($p < 0.001$). The percentage of patients who experienced CIN was significantly greater in the control group (34.3%) than in the *N*-acetylcysteine group (14.3%; $p = 0.05$). **Conclusion:** Prophylactic oral administration of *N*-acetylcysteine 1200 mg once daily for 2 days, combined with intravenous hydration, reduced the rise in serum creatinine levels over 48–72 h after the administration of the contrast agent in patients undergoing CT studies.

**Keywords:** antioxidant, contrast agent-induced, *N*-acetylcysteine, nephrotoxicity

Future Drugs Ltd

Contrast agent-induced nephrotoxicity (CIN) is the third most common cause of acute inpatient renal failure after decreased renal perfusion and postoperative renal impairment [1]. Contrast agents (CAs) reduce renal function by exerting direct toxic effects on tubular epithelial cells [2] and altering renal hemodynamics as a result of an imbalance between vasodilator and vasoconstrictor factors [1,3]. There is evidence that reactive oxygen species have a role in the development of CIN [4]. The main risk factors for CIN are pre-existing renal dysfunction, particularly that caused by diabetic nephropathy, and reduced effective arterial volume [4,5].

In patients with renal insufficiency, volume expansion has been reported to ameliorate CIN. However, administration of some previously proposed drugs, such as diuretics, calcium antagonists, theophylline, dopamine-1 receptor agonists and atrial natriuretic peptide, has not shown any effect in the prevention of CIN [1,5–7].

*N*-acetylcysteine (NAC) is proposed to be effective in the prevention of CIN due to its antioxidant properties and its ability to block the expression of vascular cell-adhesion molecule 1 [2,3,7]. Clinical studies evaluating the efficacy of NAC have yielded mixed results. Tepel and colleagues proposed oral NAC 600 mg twice daily for 2 days beginning one day before imaging [4]; however, some researchers suggest that a double oral dose of NAC (1200 mg twice daily for 2 days) may be more effective [8,9].

In this study, we assessed the effect of 2 days administration of NAC 1200 mg orally (total dose equal to that proposed by Tepel and colleagues) once daily, which is a more simple and

convenient regimen for the prevention of CIN in patients receiving CAs for abdominal and chest computed tomography (CT) studies.

## Methods

A toal of 70 patients with a known history of chronic kidney disease (serum creatinine [SCr] concentration above 1.2 mg/dl or creatinine clearance [CrCl] of less than 60 ml/min) with stable SCr during the 3 days prior to the injection of CAs were included in this prospective study. Subjects with acute renal failure or who were treated with theophylline, calcium channel blockers, dopamine receptor agonists or diuretics were excluded from the study.

Both groups were comparable in demographics, disease states, drug regimens and risk factors for developing CIN, and all patients in both groups underwent elective abdominal or CT scanning with 140 ml iohexol, a nonionic, low-osmolality CA.

The patients were randomly assigned to receive either NAC and intravenous normal saline (NAC group) or normal saline only (control group).

1000 ml of normal saline was administered intravenously to all patients at a rate of 1 ml/kg/h before contrast dye administration. 140 ml iohexol (647 mg iohexol/ iodine 300 mg/ml) was used as a CA for all patients. Additionally, subjects in the NAC group received NAC 1200 mg orally once daily on the day before imaging and at the day of CA infusion.

SCr was measured repeatedly 3 days before administration of the CA and at the day of CA administration, 24, 48 and 72 h after CA injection.

CIN was defined as an increase of at least 25% of baseline in the SCr concentration within 48–72 h after CA administration [10].

The study protocol was approved by the local ethics committee and all patients signed written informed consent form.

Levene's test for equality of variances was performed and showed no significant difference in variances between two groups. Paired t-test and independent sample t-test were used to find the differences in SCr and CrCl from baseline and between the two groups, respectively.

## Results

The clinical and biochemical characteristics of the patients in both groups are shown in **Table 1**. **Table 2** shows the p value of comparisons of SCr and CrCl at 24, 48 and 72 h after CA administration from baseline in both groups. **Table 3** presents the number of subjects who experienced CIN in each group at 24, 48 and 72 h after CA injection.

All 70 patients (35 in each group) completed the study. The causes of renal insufficiency were diabetic nephropathy in 25, nephrosclerosis in five and glomerulonephritis in five, tubulointerstitial nephritis in six patients. The underlying causes of renal failure were unknown in 29 subjects.

The mean weight of the patients in the NAC group and the control group were not statistically different (74 ± 8 and 71 ± 8 y, respectively; $p = 0.50$).

In the control group, the mean of SCr concentration increased from 1.31 ± 0.15 to 1.48 ± 0.05 mg/dl 48 h after CA injection ($p = 0.01$) and to 1.61 ± 0.01 mg/dl 72 h after administration of CA ($p < 0.001$). In the NAC group, the mean of SCr level increased from 1.43 ± 0.50 to 1.51 ± 0.01 mg/dl ($p = 0.14$) 48 h after CA infusion and to 1.45 ± 0.59 mg/dl ($p = 0.64$) 72 h after administration of CA. Change in SCr from baseline at 72 h after CA administration was significantly different between the NAC and control groups (2.42 ± 1.85 vs 23.00 ± 7.11; $p < 0.001$).

When the CrCl of patients was calculated using the modification of diet in renal disease (MDRD) formula, the mean CrCl in the control group was significantly decreased from 59.23 ± 11.54 at baseline to 50.45 ± 10.01 ml/min/1.73 $m^2$ ($p = 0.04$); however, this change was not significant in the NAC group (56.49 ± 9.11 ml/min/1.73 $m^2$ at baseline vs 55.70 ± 9.77 ml/min/1.73 $m^2$ 72 h after CA injection, $p = 0.14$).

CIN occurred in 17 of the 70 patients (24.3%). Five of the 35 patients in the NAC group (14.3%) and 12 of the 35 patients in the control group (34.3%) showed CIN.

In the NAC group, 12 patients (34%) had baseline SCr concentration above 1.5 mg/dl, as did six patients (17%) in the control group. Among patients with elevated baseline SCr, three of the 12 in the NAC group (25%) and four of six in the control group (66.7%) showed CIN.

Among the 12 patients in the control group who showed CIN 72 h after CA infusion, six (50%) showed an up to 25% rise in SCr 48 h after CA administration. Two out of five patients in the NAC group who suffered CIN showed SCr increase within 24 h after CA administration and one case experienced CIN 72 h after CA injection.

**Table 1. The clinical and biochemical characteristics of the patients.**

| Characteristic | NAC group* | Control group* | p-value |
|---|---|---|---|
| Weight (kg) | 74 ± 8 | 71 ± 8 | 0.50 |
| Age (years) | 59.76 ± 1.99 | 55.89 ± 12.92 | 0.30 |
| Sex (male/female) | 20/15 | 22/13 | 0.08 |
| Baseline SCr (mg/dl) | 1.43 ± 0.37 | 1.31 ± 0.15 | 0.15 |
| SCr 24 h after CA (mg/dl) | 1.41 ± 0.71 | 1.41 ± 0.21 | 0.21 |
| SCr 48 h after CA (mg/dl) | 1.51 ± 0.54 | 1.48 ± 0.27 | 0.19 |
| SCr 72 h after CA (mg/dl) | 1.45 ± 0.48 | 1.61 ± 0.29 | 0.09 |
| Baseline CrCl‡ (ml/min/1.73m$^2$) | 56.49 ± 11.03 | 59.23 ± 11.54 | 0.11 |
| CrCl 24 h after CA | 57.30 ± 14.61 | 57.74 ± 10.10 | 0.22 |
| CrCl 24 h after CA | 53.45 ± 14.81 | 54.96 ± 13.07 | 0.10 |
| CrCl 24 h after CA | 55.70 ± 12.97 | 50.45 ± 13.95 | 0.06 |
| Patients with CIN | 5 | 12 | 0.05 |
| Diabetic patients at baseline | 14 | 11 | 0.07 |
| Diabetic patients with CIN | 3 | 7 | 0.02 |
| Change in SCr after 24 h (%) | -2.24 ± 1.80 | 8.16 ± 4.23 | 0.06 |
| Change in SCr after 48 h (%) | 6.02 ± 2.08 | 13.11 ± 4.67 | 0.33 |
| Change in SCr after 72 h (%) | 2.42 ± 1.85 | 23.00 ± 7.11 | <0.001 |
| Change in CrCl after 24 h (%) | -12.39 ± 8.11 | -4.30 ± 2.97 | 0.30 |
| Change in CrCl after 48 h (%) | -20.45 ± 5.78 | -0.44 ± 1.07 | 0.41 |
| Change in CrCl after 72 h (%) | -9.69 ± 7.66 | -11.53 ± 4.90 | 0.04 |

**Values are presented as Mean ± SD.*

*‡CrCl based on modification of diet in renal disease formula.*

*CA: Contrast agent; CIN: Contrast agent-induced nephrotoxicity; CrCl: Creatinine clearance; NAC:* N*-acetylcysteine; SCr: Serum creatinine.*

## Discussion

The incidence of CIN varies from 0 to 90%, depending on the presence of risk factors including chronic renal insufficiency or diabetes mellitus and volume or osmolality of CA administered [11,12]. The reported incidence of CIN due to iohexol administration in patients with moderate-to-severe renal insufficiency is 19.9% [101]. All patients in this study had risk factors and received the same volume of nonionic, low-osmolality CA, iohexol, and CIN occurred in 24.3% of patients, which is in concordance with Radiological Society of North America report.

**Table 2. p-value of SCr and CrCl comparisons from baseline in both groups.**

| Paired comparisons | NAC group | Control group |
|---|---|---|
| Baseline SCr–SCr 24 h after CA | 0.15 | 0.54 |
| Baseline SCr–SCr 48 h after CA | 0.14 | 0.01 |
| Baseline SCr–SCr 72 h after CA | 0.64 | <0.001 |
| Baseline CrCl–CrCl 24 h after CA | 0.18 | 0.09 |
| Baseline CrCl–CrCl 48 h after CA | 0.10 | 0.06 |
| Baseline CrCl–CrCl 72 h after CA | 0.14 | 0.04 |

*CA: Contrast agent; CrCl: Creatinine clearance; NAC:* N*-acetylcysteine; SCr: Serum creatinine.*

The beneficial role of NAC in the prevention of CIN has been shown by some investigators [1–4,7]. It is reported that nephrotoxicities of iso-osmolality and low-osmolality contrast agents were similar when a prophylactic strategy of hydration plus NAC was used [13]. However, there are some conflicting results in the findings of some other researchers. Some studies showed no prophylactic effects of NAC in the prevention of CIN following coronary angiography in patients with moderate renal failure [14] and in patients undergoing peripheral angiography using current contrast media [15].

Although some meta-analyses supported the role of NAC in the prevention of CIN, except for the study by Tepel and colleagues that is performed in patients receiving CAs for CT scanning, the remaining trials included in these meta-analysis were on subjects receiving CAs for coronary or peripheral angiography [16–18].

**Table 3. Number of patients with CIN at 24, 48 and 72 h after CA injection.**

| | NAC group | Control group | p-value |
|---|---|---|---|
| 24 h after CA injection | 2 | 0 | 0.15 |
| 48 h after CA injection | 2 | 6 | 0.13 |
| 72 h after CA injection | 1 | 6 | 0.04 |
| Total | 5 | 12 | 0.05 |

*CA: Contrast agent; CIN: Contrast agent-induced nephrotoxicity; NAC:* N*-acetylcysteine.*

Our study showed CIN prevention with NAC in patients receiving CA for chest or abdominal CT studies.

Although some researchers suggest that a double dose of NAC (1200 mg orally twice daily for 2 days) seems to be more effective than the standard dose (600 mg orally twice daily for 2 days), especially with high volumes of a non-ionic, low-osmolality contrast agent that could be explained by dose-dependent pharmacokinetics of NAC and an increase in its bioavailability and peak serum concentration with increasing dose [8,9], most controlled studies use the standard dose of NAC. In this study, the total daily dose equal to the standard dose of NAC was used; however, because of the 30% renal elimination of NAC and some of its active metabolites, the authors suggest that the simple regimen of NAC 1200 mg once daily may be also effective in preventing CIN in subjects with chronic kidney disease.

CIN may occur beyond 48 h after CA administration; however, in previous studies, SCr levels were only monitored for 48 h after infusion of CAs. In this study, we followed subjects for 72 h after CA administration. Among those patients who showed CIN, six out of 12 in the control group (50%) showed a less than 25% increase in SCr within 48 h after CA administration. Indeed, in the NAC group, two of the five patients who suffered CIN showed a SCr rise within 24 h and another within 72 h after CA administration.

If we followed subjects for only 48 h, six patients in the control group and three patients in the NAC group could have been missed.

The main limitation of this study was the small number of subjects in each group and the lack of a placebo group. Further studies with larger patient sample sizes with renal insufficiency who were designed to undergo CT scanning are needed to confirm the results of the current study.

## Conclusion

NAC administration with a simple protocol of 1200 mg orally once daily for 2 days, along with intravenous hydration, may be proposed to prevent CIN in high-risk patients receiving CA for abdominal or chest CT studies.

### Acknowledgements

*This research was supported by Tehran University of Medical Sciences and a Health Services grant.*

**Highlights**

- We designed a study to evaluate the efficacy of 1200 mg once-daily oral administration of *N*-acetylcysteine on the day before and the day of imaging for the prevention of CIN.
- In total, 70 patients with renal insufficiency referred to our institution for abdominal or chest computed tomography scanning were randomly assigned to receive either only normal saline before contrast-agent administration (control group) or normal saline plus *N*-acetylcysteine 1200 mg single daily oral dose.
- *N*-acetylcysteine administration with a simple protocol of 1200 mg orally once daily is effective in the prevention of contrast agent-induced nephrotoxicity.
- Contrast agent-induced nephrotoxicity may occure after 48 h of contrast agent administration, therefore patients should be followed for a minimum of 72 h.

### Bibliography

1. Nash K, Hafeez A, Hou S. Hospital acquired renal insufficiency. *Am. J. Kidney Dis.* 39(5), 930–936 (2002).
2. Davidson CJ, Laskey WK, Hermiller JB *et al*. Randomized trial of contrast media utilization in high-risk PTCA. The COURT trial. *Circulation* 101, 2172–2177 (2000).
3. Russo D, Minutolo R, Cianciarus, Memoli B, Conte G, De Nicola L. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. *J. Am. Soc. Nephrol.* 6, 1451–1458 (1995).
4. 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.* 343(3), 180–184 (2000).
5. Morcos SK. Contrast media-induced nephrotoxicity – questions and answers. *Br. J. Radiol.* 71, 357–365 (1998).
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.* 331(21), 1416–1420 (1994).

7. Briguori C, Colombo A, Airoldi F *et al*. *N*-acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. *J. Am. Coll. Cardiol.* 44(4), 762–765 (2004).
8. Briguori C, Colombo A, Violante A *et al*. Standard vs double dose of *N*-acetylcysteine to prevent contrast agent induced nephrotoxicity. *Eur. Heart J.* 25, 206–211 (2004).
9. Marenzi G, Assanelli E, Marana I *et al*. *N*-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N. Engl. J. Med.* 354(26), 2773–2782 (2006).
10. Briguori C, Mangandelli F, Pierfranco S *et al*. Acetylcysteine and contrast agent-associated nephrotoxicity. *J. Am. Coll. Cardiol.* 40(2), 298–303 (2002).
11. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors and relationship to mortality. *Am. J. Med.* 103, 368–375 (1997).
12. Rudnick MR, Goldfarb S, Wexler L *et al*. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int.* 47(1), 254–261 (1995).
13. Briguori C, Colombo A, Airoldi F *et al*. Nephrotoxicity of low-osmolality versus iso-osmolality contrast agents: impact of *N*-acetylcysteine. *Kidney Int.* 68(5), 2250–2255 (2005).
14. El Mahmoud R, Le Feuvre C, Le Quan Sang KH *et al*. Absence of nephroprotective effect of acetylcysteine in patients with chronic renal failure investigated by coronary angiography. *Arch. Mal. Coeur Vaiss.* 96(12), 1157–1161 (2003).
15. Sandhu C, Belli AM, Oliveira DB. The role of *N*-acetylcysteine in the prevention of contrast-induced nephrotoxicity. *Cardiovasc. Intervent. Radiol.* 29(3), 344–347 (2006).
16. Brick R, Krzossok S, Markowetz F, Schnulle P, Van Der Woude FJ, Braun C. Acetyl cysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 362, 598–603 (2003).
17. Allonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ. Prevention of radiocontrast nephropathy with *N*-acetylcysteine in patient with chronic kidney disease: a meta-analysis of randomized, controlled trials. *Am. J. Kidney Dis.* 43, 1–9 (2004).
18. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of *N*-acetylcysteine on contrast nephropathy. *Kidney Int.* 65, 1366–1374 (2004).


## Website


101. Solomon R. Code: SSJ05–03: Genitourinary (contrast material and adverse effects) safety of low osmolar contrast media in patients with renal impairment: effects of contrast agent and premedication http://rsna2005.rsna.org


## Affiliations


*Hossein Khalili,*
*Assistant Professor of Clinical Pharmacy,*
*Department of Clinical Pharmacy,*
*School of Pharmacy,*
*Tehran University of Medical Sciences,*
*Tehran, Iran*
*Tel.: +98 912 297 9329*
*Fax: +98 216 646 1178*
*khalilih@sina.tums.ac.ir*

*Simin Dashti-Khavidaki,*
*Assistant Professor of Clinical Pharmacy,*
*Department of Clinical Pharmacy,*
*School of Pharmacy,*
*Tehran University of Medical Sciences,*
*Tehran, Iran*
*Tel.: +98 912 297 9329*
*Fax: +98 216 646 1178*

*Hamed Tabifar*
*School of Pharmacy,*
*Tehran University of Medical Sciences*
*Tehran, Iran*

*Nasrin Ahmadinejad,*
*Assistant Professor*
*Department of Radiology, Imam Hospital,*
*Tehran University of Medical Sciences,*
*Tehran, Iran*

*Farrokhlegha Ahmadi,*
*Assistant Professor*
*Department of Nephrology, Imam Hospital,*
*Tehran University of Medical Sciences,*
*Tehran, Iran*