CARDIOVASCULAR MEDICINE

N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial

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Objective: To evaluate oral *N*-acetylcysteine in the prevention of contrast induced nephropathy (CIN) in patients at low to moderate risk undergoing cardiac catheterisation with ionic low osmolality contrast medium.

Methods: In a multicentre double blind clinical trial 156 patients undergoing coronary angiography or percutaneous coronary intervention with serum creatinine $\geqslant$ 106.08 μmol/l or creatinine clearance $<$ 50 ml/min or diabetes mellitus were randomly assigned to receive *N*-acetylcysteine 600 mg orally twice daily for two days or placebo. Only low osmolality ionic contrast medium was used.

Results: Sixteen patients developed CIN, defined as an increase of 44.2 μmol/l in creatinine in 48 hours: eight of 77 patients (10.4%) in the *N*-acetylcysteine group and eight of 79 patients (10.1%) in the placebo group (p = 1.00). The mean (SD) change in serum creatinine was similar in both groups: 7.96 (35.36) μmol/l in the *N*-acetylcysteine group and 6.19 (25.64) μmol/l in the placebo group (p = 0.67). No difference was observed in the change in endogenous creatinine clearance (−0.54 (10.4) ml/min *v* −2.52 (12.3) ml/min, *N*-acetylcysteine and placebo, respectively, p = 0.28).

Conclusion: Oral *N*-acetylcysteine did not prevent CIN in patients at low to moderate risk undergoing cardiac catheterisation with ionic low osmolality contrast medium.

One of the most frequent complications of interventional cardiac procedures is contrast induced nephropathy (CIN).

The development of CIN has been associated with increases in the length of hospitalisation,[1] morbidity, and mortality.[2] Although several preventive measures have been studied,[3] only a few, such as hydration[4] and use of low osmolality contrast media,[5] have been shown to be useful. There is evidence that the two principal independent risk factors for CIN are impaired renal function and diabetes mellitus.[2]

Although the mechanisms of contrast induced renal injury are not fully understood, there is evidence that contrast media cause renal vasoconstriction[6 7] with consequent hypoxia and renal injury. In addition, free radical release, associated with exposure to contrast media, may play an important part by causing direct damage to the renal tubular epithelium.[8 9]

N-acetylcysteine has the potential to prevent CIN due to its potent antioxidant and vasodilating actions secondary to increased nitric oxide synthase expression.[7] *N*-acetylcysteine was shown to be effective in preventing CIN in non-cardiac patients with previously impaired renal function undergoing contrast enhanced computed tomography with a small volume of intravenous contrast.[10] However, in clinical trials with patients undergoing cardiac catheterisation the effects of oral *N*-acetylcysteine have not been consistently beneficial.[11–19] Recently, a meta-analysis of studies of non-ionic low osmolality contrast media suggested that *N*-acetylcysteine can be useful in preventing CIN in patients undergoing cardiac catheterisation.[20] To our knowledge, no published clinical trial has investigated the role of *N*-acetylcysteine in preventing CIN in patients undergoing radiographic procedures with an ionic low osmolality contrast media.

This was a multicentre, randomised, double blind, placebo controlled clinical trial, carried out to evaluate the effect of oral *N*-acetylcysteine on preventing CIN in patients at low to moderate risk undergoing cardiac catheterisation with the use of an ionic low osmolality contrast medium.

METHODS

Patients

Patients at risk for developing CIN who were referred for elective coronary angiography or percutaneous coronary intervention (PCI) at four Brazilian hospitals were enrolled in the present study.

Patients were considered to be at risk for developing CIN if they had one of the following criteria: serum creatinine $\geqslant$ 106.08 μmol/l, creatinine clearance (CrCl) $<$ 50 ml/min, or drug treated diabetes mellitus. Exclusion criteria were age under 18 years, use of radiographic contrast media within 21 days of randomisation, current dialysis, haemodynamic instability before the procedure (systolic blood pressure $\leqslant$ 90 mm Hg or diastolic blood pressure $\leqslant$ 60 mm Hg), and history of sensitivity to *N*-acetylcysteine.

CrCl was estimated with the Cockcroft-Gault formula, where CrCl = ([140 − age] × weight (kg)/serum creatinine (mg/dl) × 72), with adjustment for female sex ($CrCl_{female}$ = CrCl × 0.85).[21] The ethics committees of the participant centres approved the study protocol. Written informed consent was obtained from all patients.

Study protocol

Patients were randomly assigned on a 1:1 basis to receive *N*-acetylcysteine or placebo by randomly drawing sealed envelopes containing either the active drug or matching placebo. The randomisation sequence was computer

Abbreviations: CI, confidence interval; CIN, contrast induced nephropathy; CrCl, creatinine clearance; PCI, percutaneous coronary intervention

generated and was stratified by the procedure to be performed (coronary angiography or PCI). *N*-acetylcysteine and placebo envelopes were prepared by the industrial pharmacy at the headquarters (Hospital São Lucas-PUCRS). The investigators were not aware of the contents of the envelopes until the end of the study. *N*-acetylcysteine was orally administered at the dose of 600 mg twice a day, starting one day before the procedure (two doses before and two doses after the procedure). All patients received intravenous saline 0.9% 1 ml/kg/h from 12 hours before to 12 hours after exposure to the contrast medium. Serum creatinine was measured 48 hours before (baseline creatinine) and 48 hours after the procedure (post-procedure creatinine). All the procedures were performed with the low osmolality ionic contrast medium ioxaglate (Hexabrix; Guerbet Ltda, Rio de Janeiro, Brazil).

End points

The primary end points of the study were: (1) the occurrence of CIN, defined as an increase in serum creatinine $\geqslant$ 44.2 µmol/l, 48 hours after exposure to contrast medium; (2) the change in serum creatinine (post-procedure creatinine − baseline creatinine); and (3) the change in CrCl (post-procedure CrCl − baseline CrCl). Secondary end points were in-hospital death, need for haemodialysis, and length of hospitalisation.

The effect of *N*-acetylcysteine on the following predefined subgroups was also evaluated: diabetes mellitus, baseline creatinine $\geqslant$ 132.6 µmol/l, and volume of the contrast medium used in the procedure $\leqslant$ 1.5 ml/kg.

Statistical analysis

Categorical variables were compared by the χ^2 test or Fischer's test. Continuous variables were compared by two tailed unpaired Student's *t* test. Data are expressed as mean (SD). For variables with non-parametric distribution, the Mann-Whitney test was used and data are expressed as median (25th to 75th centile). Multivariate analysis was performed to adjust for the difference in baseline creatinine between groups by assessing the primary outcomes.

On the basis of an expected 10% incidence of CIN in this study population,[12 14] a two tailed significance level of 0.05, and a statistical power of 80%, a sample size of 156 patients would be required to detect a 50% change in the relative risk for CIN associated with the active treatment. Data were analysed with SPSS software, version 10.1 (SPSS Inc, Chicago, Illinois, USA).

Table 2 Incidence of contrast medium induced nephropathy and changes in serum creatinine and clearance of endogenous creatinine from baseline to 48 hours after contrast medium exposure

	N-acetylcysteine (n = 77)	Placebo (n = 79)	p Value
Incidence of CIN	8 (10.4%)	8 (10.1%)	1.00
Change in creatinine (µmol/l)	7.96 (35.36)	6.19 (25.64)	0.67
Change in CrCl (ml/min)	−0.43 (10.6)	−2.82 (12.0)	0.19

Values are mean (SD).
CIN, contrast induced nephropathy.

RESULTS

From April 2001 to April 2003, 156 patients were enrolled in the study to receive *N*-acetylcysteine (77 patients) or placebo (79 patients). Table 1 shows the baseline clinical characteristics and procedure related variables. The mean (SD) baseline serum creatinine and CrCl of the study population were 117.57 (39.78) µmol/l and 60.9 (29.5) ml/min, respectively.

Groups were well balanced with respect to age, sex, body mass index, blood pressure, diabetes mellitus, and drug treatment. In the placebo group, serum creatinine was

Table 3 Secondary outcomes

	N-acetylcysteine (n = 77)	Placebo (n = 79)	p Value
Length of hospitalisation (days)	6 (2–13)	5 (2–10)	0.44
Haemodialysis (n)	2	0	0.24
Death (n)	5	2	0.42

The numbers in parentheses are the 25th and 75th centiles.

Table 1 Baseline clinical characteristics and procedure related variables

	N-acetylcysteine (n = 77)	Placebo (n = 79)	p Value
Age (years)	63.8 (11.30)	66.5 (11.1)	0.14
Male sex (%)	61.0	57.0	0.72
Body mass index (kg/m^2)	27.0 (4.74)	28.1 (4.93)	0.14
Creatinine (µmol/l)	123.76 (45.08)	111.38 (30.94)	0.05
CrCl (ml/min)	59.0 (27.4)	62.9 (31.1)	0.41
Blood pressure (mm Hg)			
Systolic	131.8 (19.4)	131.3 (23.2)	0.90
Diastolic	76.7 (12.4)	77.6 (11.3)	0.63
Hypertension	87.0%	84.8%	0.86
Diabetes mellitus	51.9%	51.9%	1.00
Drugs in use			
Diuretics	41.6%	51.9%	0.25
Calcium channel blocker	10.4%	15.2%	0.51
ACE inhibitor	70.1%	68.4%	0.94
Angiographic findings			0.52
Non-obstructive disease	12.9%	14.0%	
Single vessel disease	21.4%	31.0%	
Double vessel disease	28.6%	26.8%	
Triple vessel disease	37.1%	28.2%	
LVEF (%)	55.3	59.4	0.30
Cardiac angiographic procedure			1.00
Coronary angiography	76.7%	77.3%	
Percutaneous intervention	23.3%	22.7%	
Contrast volume (ml)	102.5 (47.3)	102.8 (60.4)	0.97

Values are mean (SD) or percentage.
ACE, angiotensin converting enzyme; CrCl, estimated creatinine clearance; LVEF, left ventricular ejection fraction.

slightly lower, with a borderline significance (111.38 (30.94) *v* 123.76 (45.08) μmol/l, p = 0.05). However, the estimated CrCl was similar in both groups (62.9 (31.1) *v* 59.0 (27.4) ml/min, p = 0.41, respectively, for placebo and *N*-acetylcysteine). The volume of contrast used during the procedure and the proportion of coronary angiography and PCIs were similar in the groups. No adverse reaction to the study drug was reported.

Primary end points

The incidence of CIN was similar in both groups, as well as the change in serum creatinine and CrCl (table 2). After adjustment for baseline creatinine by logistic regression and multiple linear regression, as appropriate, the primary outcomes remained unchanged.

Secondary end points

No difference was observed between the groups regarding the secondary end points (table 3). The length of hospitalisation, need for haemodialysis, and incidence of in-hospital death were similar between groups. During the same hospitalisation 14 patients in the *N*-acetylcysteine group and 10 in the placebo group underwent coronary artery bypass graft surgery after the cardiac catheterisation. Seven (4.6%) patients died, five in the *N*-acetylcysteine group and two in the placebo group. In the *N*-acetylcysteine group, two (1.2%) deaths were associated with the development of CIN and occurred in patients requiring haemodialysis. The three other deaths in the *N*-acetylcysteine group were caused by stroke (one patient) and by postoperative complications of coronary artery bypass graft surgery (two patients). In the placebo group, one death was related to pulmonary thromboembolism and the other was associated with postoperative complications of coronary artery bypass graft surgery.

Analysis of subgroups

N-acetylcysteine provided no significant effect in any of the subgroups analysed (table 4). Among the 46 patients with serum creatinine ⩾ 132.6 μmol/l, the incidence of CIN was 15.4% in the *N*-acetylcysteine group and 20.0% in the placebo group (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.15 to 3.35; p = 0.71).

Among the 81 patients with diabetes mellitus, the incidence of CIN was 10.0% in the *N*-acetylcysteine group and 9.8% in the placebo group (OR 1.02, 95% CI 0.27 to 4.42; p = 1.00).

Among the 96 patients receiving a low volume of contrast (⩽ 1.5 ml/kg), the incidence of CIN in the *N*-acetylcysteine and placebo groups was 11.4% and 9.6%, respectively (OR 1.20, 95% CI 0.32 to 4.46; p = 1.00).

DISCUSSION

This is the first double blind, multicentre, randomised study assessing the effect of *N*-acetylcysteine in preventing CIN in a population at low to moderate risk undergoing cardiac catheterisation with an ionic low osmolality contrast medium. Our findings indicate that oral *N*-acetylcysteine does not provide any benefit as compared with placebo to reduce the incidence of CIN in this patient population. In addition, the use of *N*-acetylcysteine was not beneficial in any of the predefined subgroups of patients with diabetes, creatinine > 132.6 μmol/l, and contrast volume < 1.5 ml/kg. The lack of a beneficial effect of *N*-acetylcysteine was confirmed by multivariate analysis with control for the difference in the creatinine concentration before the procedure.

The initial study by Tepel and colleagues,[10] reporting that *N*-acetylcysteine reduced the incidence of CIN in patients undergoing computed tomography, generated considerable enthusiasm regarding this low cost and easy to use drug. That study randomised treatment of 83 patients who had serum creatinine ⩾ 106.08 μmol/l (or CrCl < 50 ml/min) undergoing computed tomography with a small fixed intravenous contrast medium volume of 75 ml and found an impressive 90% reduction in the relative risk of CIN. After that study, additional clinical trials carried out in patients undergoing coronary angiography, PCI, or both had, however, controversial results.[11–19] Although in a meta-analysis *N*-acetylcysteine has been shown to prevent CIN in patients with renal functional impairment undergoing cardiac catheterisation, the absence of small negative trials is a possible bias that may have influenced these findings as recognised by the authors.[20] In addition, a recent systematic review by Kshirsagar and colleagues[22] suggested that the role of *N*-acetylcysteine in the prevention of CIN has yet to be defined.

The conflicting results between our study and previous studies may also be explained by the differences in the contrast media used. Our investigation was conducted with an ionic low osmolality contrast medium, which is used in almost half of PCIs performed outside the USA.[23] All others studies used non-ionic contrast media. In experimental studies, ionic low osmolality contrast media and non-ionic contrast media have caused different degrees of renal hypoxia and structural damage in the tubule cells.[24 25] It is conceivable that *N*-acetylcysteine has distinctive effects on preventing nephrotoxicity caused by various contrast agents.

In the present study the serum baseline creatinine concentration in the placebo group was slightly lower, with a borderline significance, than in the *N*-acetylcysteine group, although the estimated CrCl was similar in both groups. We assume that baseline creatinine concentrations did not influence the effect of *N*-acetylcysteine as indicated by multivariate analysis.

The incidence of CIN in our investigation of patients with moderate renal failure (mean baseline creatinine 117.57 μmol/l) was 10.3%, similar to that found in other studies of patients at risk.[11 14] These patient characteristics do not allow us to draw definite conclusion about the effect of *N*-acetylcysteine on very high risk patients (creatinine ⩾ 176.8 μmol/l), even with the subgroup and multivariate analysis performed. However, considering that only 4% of the population undergoing cardiac catheterisation has serum creatinine concentrations above 176.8 μmol/l,[2] the present findings can be applied to the majority of patients undergoing cardiac catheterisation at risk for developing CIN.

Table 4 Incidence of CIN in the predefined subgroups

	Number	*N*-acetylcysteine	Placebo	OR	95% CI	p Value
Diabetes mellitus	81	10.0%	9.8%	1.02	0.27 to 4.42	1.00
No diabetes mellitus	75	10.8%	10.5%	1.03	0.23 to 4.46	1.00
Creatinine ⩾132.6 μmol/l	46	15.4%	20.0%	0.72	0.15 to 3.35	0.71
Creatinine <132.6 μmol/l	110	7.8%	6.8%	1.17	0.27 to 4.93	1.00
Contrast ⩽1.5 ml/kg	96	11.4%	9.6%	1.20	0.32 to 4.46	1.00
Contrast >1.5 ml/kg	60	9.4%	11.5%	0.79	0.14 to 4.30	1.00

CI, confidence interval; OR, odds ratio.

The dose and route of administration of *N*-acetylcysteine in our study were the same as those in the majority of previous studies: 600 mg orally every 12 hours for two days, beginning the day before the procedure. Recently, intravenous administration of *N*-acetylcysteine has been shown to be effective in an initial study of only 80 patients.[26] However, a larger clinical trial with 425 patients did not find a benefit.[27]

Secondary end points

Once the rise of creatinine is a surrogate end point, we also investigated the effect of oral *N*-acetylcysteine on hard clinical end points (in hospital death, length of hospitalisation, and need for haemodialysis). The study of Kay and colleagues[14] was the only one that investigated the length of hospital stay as a secondary end point. Our study did not shown any benefit of *N*-acetylcysteine on in-hospital death, need for dialysis, and length of hospital stay. The high in-hospital mortality observed in this study may be explained by the high cardiovascular risk of the patients. More than half of the study patients had multivessel disease and some patients underwent surgical revascularisation during the study period.

Subgroups

N-acetylcysteine was not effective in preventing CIN in any of the predefined subgroups. Diabetes mellitus is a well known independent risk factor for CIN.[2 28] Post hoc analysis of a previous study indicated that *N*-acetylcysteine may effectively prevent CIN in patients with diabetes.[14] In our study the predefined subgroup analysis of 81 diabetic patients indicated that *N*-acetylcysteine was not effective, independently of the presence or absence of diabetes mellitus. In another post hoc analysis,[12] *N*-acetylcysteine provided protection for patients receiving < 140 ml of contrast medium during angiography. Our study did not confirm this finding.

Clinical implications

This is the first multicentre study evaluating the role of oral *N*-acetylcysteine in preventing CIN in patients undergoing cardiac catheterisation with an ionic low osmolality contrast medium. Our major finding was that *N*-acetylcysteine did not prevent acute renal failure in patients at low to moderate risk of CIN.

On the basis of these findings, we believe that the use of *N*-acetylcysteine to prevent CIN in this patient population should not be encouraged. The recommended measures for preventing CIN continue to be appropriate hydration and the use of a small volume of contrast in patients at low to moderate risk of CIN undergoing cardiac catheterisation with an ionic low osmolality contrast medium remain.

Limitation of the study

A potential limitation of this study was that serum creatinine was only measured 48 hours after the procedure. Although most clinical trials on preventive measures for CIN have assessed creatinine during that period and creatinine usually increases 24 hours after exposure and peaks within 48–72 hours, a later increase in serum creatinine may have passed unnoticed in some patients. The CrCl was estimated by the Cockcroft-Gault formula, which is widely used in clinical practice and in clinical trials; however, it is not a formal measurement of CrCl.

The study sample size was calculated aiming at reaching statistical difference in primary outcomes. Therefore, although no trends were observed in the subgroups, our study has a limited statistical power for this analysis.

Conclusion

The use of *N*-acetylcysteine was not effective in preventing CIN in patients at low to moderate risk undergoing cardiac catheterisation with an ionic low osmolality contrast medium.

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IMAGES IN CARDIOLOGY

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Transoesophageal echocardiography for the identification of a giant aortic thrombus

A 76 year old man presented with severe abdominal pain, vomiting, and signs of lower right limb ischaemia. The patient had no previous medical history but smoked cigarettes. The ECG and transthoracic echocardiography showed no significant abnormality. Computerised tomography of his abdomen demonstrated multiple renal and splenic infarcts. The patient underwent emergency right femoral embolectomy and was anticoagulated with intravenous heparin.

A transoesophageal echocardiogram was requested. This revealed a normal heart with no evidence of intracardiac shunt. The descending aorta was visualised at the end of the procedure and there was a large pedunculated thrombus measuring 4 × 2 cm (panel A, video clip 1) (to view video footage, visit the *Heart* website—http://www.heartjnl.com/supplemental). Thrombolysis was considered, but in view of the risk of precipitating further emboli, the patient was anticoagulated with warfarin. The patient remained free from further embolic events. Transoesophageal echocardiography three months later revealed a smooth, posteriorly located plaque in the descending aorta (fig 2) with no evidence of residual thrombus.

This report demonstrates the additional value of transoesophageal echocardiography in identifying a source of arterial embolisation. It is recognised that aortic atheromatous plaques are a potential source of embolism. Overlying aortic thrombi are a rare but potentially underestimated source of systemic emboli. Undiagnosed and untreated, they may have catastrophic consequences. In this case, although transthoracic echocardiography was normal, a giant thrombus in the descending aorta was found on a transoesophageal study. Transoesophageal echocardiography should be considered when there is high level of suspicion of a cardiac source of embolism.

To view video clip visit the *Heart* website—http://www.heartjnl.com/supplemental

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