Prevention of Radiocontrast-induced Nephropathy with N-acetylcysteine After Cardiac Angiography in Diabetic Patients with Renal Dysfunction

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Purpose. To examine the effects of N-acetylcysteine (NAC) in a homogeneous high-risk population.

Methods. This is a prospective randomized single-blinded placebo-controlled clinical study. Diabetic patients with pre-existing renal insufficiency (serum creatinine concentration (SCC) above 1.6 mg/dL, or estimated creatinine clearance (CCR) less than 40 mL/min) who had received moderate to large amounts of non-ionic low osmolar contrast medium, Omnipaque (iohexol), during a diagnostic or interventional procedure were eligible to participate. All patients were adequately hydrated with half-saline (1 mL/(kg·h) from 12 hours before to 12 hours after the procedure). They were randomized into one of two groups. Patients in the NAC group were given NAC 600 mg orally twice a day, 4 doses in total; the first dose was given one day before the procedure. Patients in the control group were given placebo orally twice a day, 4 doses in total; the first dose was given one day before the procedure. SCC was assessed before hydration, 2 days after the procedure, and 5 days after the procedure. Radiocontrast-induced nephropathy (RCIN) was defined as a 25% rise from baseline or an absolute increase of 0.5 mg/dL in SCC after the procedure. The primary end-point was risk of developing RCIN.

Results. Twenty patients completed the study. There were no significant differences in age, sex, body mass index, blood pressure, duration of angiography, or mean volume of dye infused between the two groups. CCR did not change significantly in either group 2 days after angiography (NAC group 24.5 ±10.3 *vs* 29.6 ±10.6 mL/min, N = 11 , $p = 0.34$; control group 27.4 ±10.3 *vs* 29.6 ±10.6 mL/min, N = 9, $p = 0.57$), or 5 days after angiography (NAC group 24.5 ±10.3 *vs* 27.4 ± 11.8 mL/min, N = 11, $p = 0.40$; control group 27.4 ±10.3 *vs* 24.2 ±8.8 mL/min, N = 9, $p = 0.43$). None of the patients in the NAC group and five patients in the control group developed RCIN. The incidence of RCIN was lower in the NAC group (0% *vs* 56%, $p = 0.006$, N = 20). The average length of hospitalization was shorter in the NAC group (5.2 *vs* 8.1 days, $p = 0.04$, N = 20). None of the patients who developed RCIN required dialysis.

Conclusion. NAC protects diabetic patients with renal dysfunction from iohexol-related RCIN after cardiac angiographic procedures. **(Mid Taiwan J Med 2007;12:173-83)**

Key words

cardiac angiography, N-acetylcysteine, radiocontrast-induced nephropathy

INTRODUCTION

Radiocontrast-induced deterioration in renal function was first reported by Pendergrass et al in 1942 [1]. Various studies have confirmed that

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radiocontrast-induced nephropathy (RCIN) increases in-hospital morbidity and mortality, prolongs hospital stay, and results in increased costs [2-4]. The incidence of RCIN ranges from 1% in previously healthy patients to more than 50% in high-risk groups [5-7]. The three major risk factors of RCIN are pre-existing renal insufficiency, diabetes mellitus and dehydration [8-10]. In diabetic patients with serum creatinine concentrations (SCC) ranging from 2.0 mg/dL to 4.0 mg/dL, the incidence of RCIN is approximately 30%, and in those with SCC above 4.0 mg/dL, the incidence of RCIN may reach 80% [11]. In another study assessing diabetic patients with azotemia undergoing coronary angiography, 50% of the patients had a 25% increase in SCC and 12% of them required hemodialysis [12].

However, optimal therapy to prevent RCIN remains uncertain. Two means have been identified to be helpful in preventing RCIN and are now applied routinely. They are adequate hydration [4,13] and the use of non-ionic low-osmolar contrast medium [14]. Other drugs that have been studied are not consistently beneficial or may even be harmful, including furosemide, mannitol, dopamine, calcium channel blockers, atrial natriuretic peptide and aminophylline [4,13-20]. In 2000, Tepel et al found that prophylactic oral administration of the antioxidant N-acetylcysteine (NAC) before performing CT scan in patients with chronic renal insufficiency prevented the reduction in renal function induced by iopromide, a nonionic, low-osmolar contrast agent [21]. However, the amount of contrast media they used was small (75 mL in each patient).

Three reports evaluated the renoprotective effect of NAC in patients with pre-existing renal insufficiency undergoing coronary angiography and/or angioplasty using higher doses of low-osmolar radiocontrast. Briguori et al found that the amount of contrast agent, but not the administration of prophylactic NAC, was a predictor of renal function deterioration [22]. Kay et al concluded that NAC prevents RCIN with minimal adverse effects and at a low cost [23]. Boccalandro et al concluded that the effect of N-acetylcysteine is not better than hydration alone [24]. Because of the difference in study designs and the inclusion of diabetic as well as non-diabetic patients, no final conclusion can be reached about whether NAC can prevent RCIN in diabetic patients with renal insufficiency. We performed a prospective, randomized, single-blinded, placebo-controlled trial to determine whether oral NAC can prevent RCIN in diabetic patients with pre-existing renal insufficiency during cardiac angiography.

SUBJECTS AND METHODS

Study Subjects

Patients with diabetes mellitus and an elevated HbA1c, baseline SCC $\geq$ 1.6 mg/dL or estimated creatinine clearance (CCR) < 40 mL/min, who had undergone cardiac angiography at the China Medical University Hospital for diagnostic or therapeutic procedures, and received a volume of radiocontrast (iohexol) greater than 1.5 mL/kg were eligible to participate. CCR was calculated from SCC using the Cockcroft-Gault formula, CCR = (140-age) $\times$ body weight (kg) / SCC $\times$ 72; female gender adjustment was multiplied by 0.85 [25]. Patients were enrolled from July 2003 to July 2005. Exclusion criteria included age less than 18 years, shock, unstable renal function (including end stage renal disease), active urinary tract infection, acute renal failure or dialysis within the previous 30 days, heavy proteinuria (urinary protein $\geq$ 300 mg/dL in spot urine) or gross hematuria, active congestive heart failure, left ventricular ejection fraction < 40% by M-mode echocardiography, acute coronary syndrome requiring immediate intervention, exposure to contrast media or other nephrotoxic agents within the previous 30 days, exposure to contrast media other than iohexol, or exposure to aminophylline, dopamine or mannitol from one week before the procedure until the end of the study. Patients were also excluded if serum creatinine measurements varied by more than 15% thirty days prior to angiography. The study protocol was approved by the hospital's

Institutional Review Board and all patients gave written informed consent.

Study design

Eligible patients were randomized to either the NAC group (NAC plus conventional therapy) or control group (placebo plus conventional therapy) based on random numbers generated by computer. All patients were admitted to hospital the day before the index procedure. Conventional therapy consisted of hydration with 0.45% saline intravenously at a rate of 1 mL/(kg•h), 12 hours before to 12 hours after the procedure. Patients were observed for the development of congestive heart failure during this period. Renal echo was performed to evaluate the size of both kidneys and to exclude other possibilities of renal insufficiency (renal stone, hydronephrosis) Patients were randomized to receive either 4 doses of NAC (600 mg/twice a day, 2 doses before and 2 doses after the procedure) or 4 doses of placebo. The placebo capsule looked identical to that containing NAC but was empty. Oral hypoglycemic agents or insulin was given as indicated, but metformin was withheld because of its potential toxic accumulation if acute contrast nephropathy developed. Diuretics were avoided if possible.

Coronary angiography and/or angioplasty were carried out as standard procedures. All catheterization procedures were performed with the same radiocontrast, Omnipaque (iohexol; Amersham Health Inc., Princeton, NY, USA; more than 1.5 mL/kg). Abdominal aortography was performed with a pig-tail catheter at the end of catheterization to exclude renal artery stenosis. Neither selective renal angiography nor renal artery angioplasty was performed. Patients were excluded from the study if the amount of contrast medium was less than 1.5 mL/kg.

Data collection

Demographic information was gathered at baseline and included age, gender, a review of systems to identify those with a prior history of hypertension, congestive heart failure, and identification of medications being taken. Other pertinent data collected were patient's weight, indication for cardiac catheterization, blood pressure, record of any dye exposure over the preceding four weeks, and laboratory data (SCC within 30 days, complete blood count, comprehensive metabolic profile, SCC, and urinalysis prior to catheterization). Following catheterization, data recorded included any side effects due to NAC, blood urea nitrogen, SCC at day 2 and day 5 following exposure to radiocontrast, and total volume of contrast medium administered.

Statistical analysis

The final analysis was conducted on an intention-to-treat basis. Categorical variables were analyzed by the chi-square test. Differences in SCC and CCR among stages between the two groups were analyzed by the nonparametric Mann-Whitney test. Since the sample size was small, the Mann-Whitney test was used because of its higher asymptonic relative efficiency (ARE) [26]. The duration of hospitalization was analyzed by the Student's t test. Analyses were performed with SPSS software (release 12.0, SPSS, Chicago). All statistical tests were two-tailed. A p value less than 0.05 was considered significant.

RESULTS

From July 2003 to July 2005, a total of 2846 patients were referred to the China Medical University Hospital for cardiac catheterization, including diagnostic and interventional procedures. However, due to the introduction of a non-ionic iso-osmolar contrast medium, Visipaque, which is less nephrotoxic than the non-ionic low-osmolar contrast medium, Omnipaque [27], our trial was forced to be terminated under a consideration of ethics. Therefore, only twenty patients were included in the study. Baseline characteristics of studied patients are presented in Table 1. There were no significant differences in age, sex, body mass index, blood pressure, duration of angiography, HbA1c level, and mean volume of dye infused between the two groups. However, in the control group, more patients had a history of stroke and received more angiotensin converting enzyme inhibitors (ACEi) and diuretics than patients in the NAC group. In the NAC group, patients had

Table 1. Baseline characteristics

Characteristics	Total (N = 20)	NAC (N = 11)	Control (N = 9)
Age (yr), range	44-84	44-84	48-78
Body mass index, range	21.6-33.2	21.6-33.2	24.4-33.2
Male/Female	10/10	7/4	3/6
Systolic blood pressure (mmHg)	147.0 ± 4.0*	150.0 ± 5.0	144.0 ± 5.0
Diastolic blood pressure (mmHg)	72.0 ± 2.0	74.0 ± 3.0	70.0 ± 2.0
HbA1C (%)	8.3 ± 1.5	8.3 ± 1.5	8.3 ± 1.7
Procedure duration (min)	55.3 ± 23.5	55.6 ± 24.3	45.6 ± 9.2
Dye volume (mL)	188.6 ± 57.9	206.5 ± 67.5	166.7 ± 35.8
Volume of hydration (mL)	1920.0 ± 316.6	1932.7 ± 314.8	1904.4 ± 337.1
Abdominal angiography, n (%)	7.0 (35.0)	3.0 (27.0)	4.0 (44.0)
Procedure types, n (%)			
PCI	18.0 (90.0)	10.0 (91.0)	8.0 (89.0)
Diagnosis	2.0 (10.0)	1.0 (9.0)	1.0 (11.0)
Hypertension, n (%)	18.0 (90.0)	9.0 (82.0)	9.0 (100.0)
Hyperlipidemia, n (%)	11.0 (55.0)	7.0 (64.0)	4.0 (44.0)
Previous MI, n (%)	2.0 (10.0)	1.0 (9.0)	1.0 (11.0)
Previous CABG, n (%)	2.0 (10.0)	1.0 (9.0)	1.0 (11.0)
CHF, n (%)	1.0 (5.0)	1.0 (9.0)	0.0 (0.0)
Previous stroke, n (%)	4.0 (20.0)	1.0 (9.0)	3.0 (33.0)
Medications, n (%)			
Calcium channel blockers	8.0 (40.0)	7.0 (64.0)	1.0 (11.0)
Aspirin	18.0 (90.0)	9.0 (82.0)	9.0 (100.0)
ACE inhibitor	7.0 (35.0)	2.0 (18.0)	5.0 (56.0)
ARB	6.0 (30.0)	3.0 (27.0)	3.0 (33.0)
Statin	10.0 (50.0)	7.0 (64.0)	3.0 (33.0)
Diuretics	12.0 (60.0)	5.0 (45.0)	7.0 (78.0)

*Mean ± SD. There is no significant difference between NAC and control groups in all characteristics ($p > 0.05$). NAC = N-acetylcysteine; HbA1c = glycosylated hemoglobin; PCI = percutaneous coronary intervention; MI = myocardial infarction; CABG = coronary artery bypass graft; CHF = congestive heart failure; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker.

more hyperlipidemia and received more calcium channel blockers and statin than patients in the control group. Renal echo did not disclose renal stone or hydronephrosis in the study group. Renal artery stenosis was not identified during abdominal aortography. The potential cause of renal insufficiency was attributed to diabetic nephropathy in all patients.

All of our patients continued to take ACEi and angiotensin II receptor blockers (ARB) during the study. In the NAC group, 6 patients received insulin therapy and 5 patients took oral hypoglycemic agents. Three patients had taken metformin, but it was withheld since the day of the index procedure. In the control group, 4 patients received insulin therapy and 5 patients took oral hypoglycemic agents. Metformin had been given to 2 patients, but it was withheld since the day of the index procedure. We did not shift metformin to insulin use in either group. In the NAC group, 3 patients received loop diuretics, 2 patients received thiazides, and 2 patients received potassium-sparing diuretics before the study. In the control group, 3 patients received loop diuretics and 4 patients received thiazides before the study. All of the diuretics were withheld since the day of the index procedure in both groups. No patients experienced active congestive heart failure during the study after discontinuation of diuretics.

The duration of cardiac angiography and volume of infused contrast were 55.3 ± 23.5 minutes and 188.6 ± 57.9 mL, respectively. There were no significant differences between the two groups in duration of angiography (NAC 55.6 ± 24.3 minutes and control 45.6 ± 9.2 minutes, p =

0.15) or volume of contrast used (NAC 206.5 ± 67.5 mL and control 166.7 ±35.8 mL, p = 0.19) (Table 1). The volume of hydration was 1920.0 ± 316.6 mL. Both groups received similar amounts of hydration (mean volume of hydration NAC 1932.7 ±314.8 mL, control 1904.4 ± 337.1 mL, p = 0.999). The blood pressure did not change significantly after the procedure in the NAC group (systolic blood pressure 150 ± 5 mmHg and 147 ±4 mmHg, p = 0.37; diastolic blood pressure 74 ± 3 mmHg and 72 ± 2 mmHg, p = 0.47) or the control group (systolic blood pressure 144 ± 5 mmHg and 140 ±13 mmHg, p = 0.38; diastolic blood pressure 70 ± 2 mmHg and 76 ± 9 mmHg, p = 0.16). None of our patients experienced shock, unstable hemodynamics, acute congestive heart failure, or acute coronary syndrome. None of the patients required temporary hemodialysis during the study and no adverse events were recorded after NAC administration.

The clinical outcomes are given in Table 2. None of the patients in the NAC group developed RCIN 5 days after administration of contrast medium. Five patients in the control group experienced RCIN 5 days after angiography. The rate of RCIN was lower in the NAC group (0% *vs* 56%, p = 0.006, N = 20). The average length of hospitalization was shorter in the NAC group (5.2 *vs* 8.1 days, p = 0.04, N = 20). None of the patients who developed RCIN required dialysis.

Table 3 shows the values of SCC and CCR 30 days before admission (SCC1, CCR1), on the day before angiography (SCC2, CCR2), 2 days after angiography (SCC3, CCR3), and 5 days after angiography (SCC4, CCR4). There were no differences in changes of SCC1-SCC2 and CCR1-CCR2 between the two groups, reflecting stable renal function before angiography (Table 4). The changes in serum urea nitrogen concentrations were similar to those in SCC. SCC did not change significantly in either group 2 days after angiography (NAC group 2.9 ± 0.9 *vs* 2.5 ± 0.9 mg/dL, N = 11 , p = 0.28; control group 2.6 ± 0.8 *vs* 2.4 ±0.7 mg/dL, N = 9, p = 0.51), and 5 days after angiography (NAC group 2.9 ± 0.9 *vs* 2.6 ±0.8 mg/dL, N = 11 , p = 0.28; control group 2.6 ± 0.8 *vs* 2.9 ±0.8 mg/dL, N = 9, p = 0.40). CCR did not change significantly in either group 2 days after angiography (NAC group 24.5 ±10.3 *vs* 29.6 ±10.6 mL/min, N = 11 , p = 0.34; control group 27.4 ± 10.3 *vs* 29.6 ±10.6 mL/min, N = 9, p = 0.57), and 5 days after angiography (NAC

Table 2. Clinical outcomes in N-acetylcysteine (NAC) and control groups

Outcomes	NAC (N = 11)	Control (N = 9)	p
RCIN (5 days), n (%)*	0.0 (0.0)	5.0 (56.0)	0.006
Length of hospitalization days, mean ±SD†	5.2 ±1.5	8.1 ±4.1	0.04

*Chi-square analysis. †Student's t test analysis.

Table 3. Values of serum creatinine concentration (SCC) and estimated creatinine clearance (CCR) in different stages in N-acetylcysteine (NAC) and control groups

	Total (N = 20)	NAC (N = 11)	Control (N = 9)	p*
SCC1	2.7 ±1.0†	2.8 ±1.0	2.5 ±1.0	0.46
SCC2	2.7 ±0.8	2.9 ±0.9	2.6 ±0.8	0.71
SCC3	2.5 ±0.8	2.5 ±0.9	2.4 ±0.7	0.90
SCC4	2.7 ±0.8	2.6 ±0.8	2.9 ±0.8	0.41
CCR1	27.4 ±11.8	26.4 ±13.4	28.5 ±10.3	0.33
CCR2	25.8 ±9.8	24.5 ±10.3	27.4 ±10.3	0.50
CCR3	29.5 ±12.8	29.6 ±10.6	29.6 ±10.6	0.83
CCR4	26.0 ±10.4	27.4 ±11.8	24.2 ±8.8	0.66

*Comparison between NAC and control groups. †Data are presented as mean ±SD. SCC1, CCR1 = SCC and CCR within 30 days before angiography; SCC2, CCR2 = SCC and CCR at admission; SCC3, CCR3 = SCC and CCR at 2 days; SCC 4, CCR4 = SCC and CCR at 5 days.

group 24.5 ± 10.3 *vs* 27.4 ± 11.8 mL/min, N = 11, p = 0.40; control group 27.4 ± 10.3 *vs* 24.2 ± 8.8 mL/min, N = 9, p = 0.43). The individual values of SCC the day before angiography (SCC2), 2 days after angiography (SCC3), and 5 days after angiography (SCC4) are illustrated in Figure.

Table 4 shows the changes in SCC and CCR during different stages in our study. The changes in SCC and CCR were insignificant in both groups. However SCC decreased and CCR increased between baseline and day 2 (SCC2-3, p = 0.28; CCR2-3, p = 0.34), baseline and day 5 (SCC2-4, p = 0.28; CCR2-4, p = 0.40) in the NAC group. These changes in SCC and CCR in the control group only occurred between the second day and and the fifth day after admission (SCC3-4, p = 0.16; CCR3-4, p = 0.20) and were not be seen among other stages. The difference in changes of SCC and CCR in both groups was highest between baseline and 2 days after baseline (SCC2-3, p = 0.18; CCR2-3, p = 0.32).

DISCUSSION

Radiographic contrast media account for 10% of all causes of hospital-acquired acute renal failure and represent the third most common cause of in-hospital renal function deterioration after decreased renal perfusion and postoperative renal insufficiency [2]. The in-hospital mortality rate in patients developing renal insufficiency is directly related to the magnitude of the increase in the serum creatinine concentration [16,28,29]. The mortality rate ranges from 3.8% with an increase in serum creatinine of 0.5 to 0.9 mg/dL

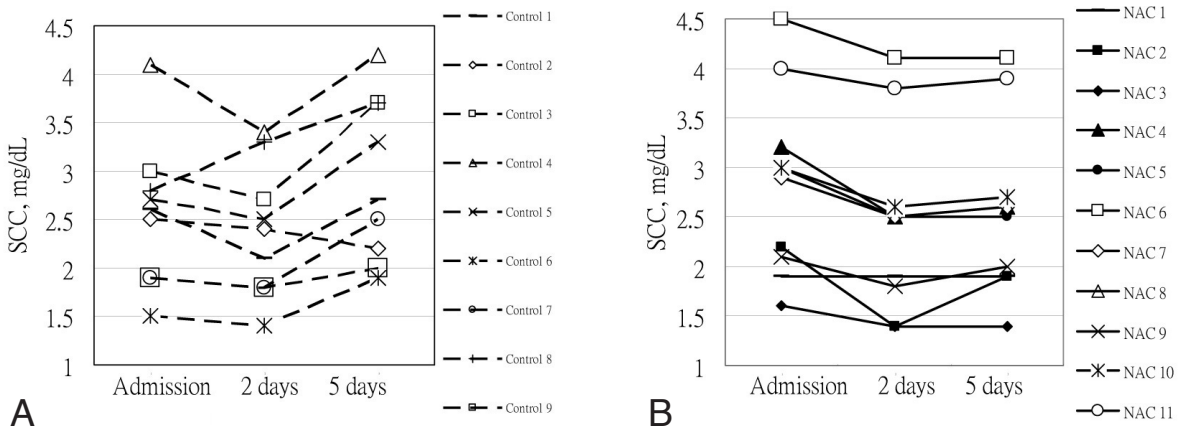

Figure. Changes from pre-angiography to 2 days and 5 days post-angiography levels of serum creatinine in individual patients. A: Control. B: NAC group.

Table 4. Multiple comparisons on the changes of serum creatinine concentration (SCC) and estimated creatinine clearance (CCR) in different stages in N-acetylcysteine (NAC) and control groups

Comparisons	p		
	NAC* (N = 11)	Control* (N = 9)	Total† (N = 20)
SCC1-SCC2	0.97	0.69	0.82
CCR1-CCR2	0.92	0.79	0.76
SCC2-SCC3	0.28	0.51	0.18
CCR2-CCR3	0.34	0.57	0.32
SCC3-SCC4	0.49	0.16	0.20
CCR3-CCR4	0.74	0.20	0.34
SCC2-SCC4	0.28	0.40	0.83
CCR2-CCR4	0.40	0.43	0.98

*The previous and the next stages were compared. †Differences of the previous and the next stages of two groups were compared. SCC1, CCR1 = SCC and CCR within 30 days before angiography; SCC2, CCR2 = SCC and CCR at admission; SCC3, CCR3 = SCC and CCR at 2 days; SCC 4, CCR4 = SCC and CCR at 5 days.

to 64% with an increase of > 3 mg/dL [11]. Prevention of RCIN will provide significant public health benefits because it will reduce the in-hospital mortality rate, hospital stay and need for dialysis.

Debate continues on whether NAC can prevent contrast-nephropathy in high risk patients. A meta-analysis of the most currently available randomized data concerning NAC before coronary angiography to prevent RCIN in patients with impaired renal function is not conclusive and does not provide proof beyond a reasonable doubt to influence clinical practice and public policy [30]. The objective of this study was to determine whether oral NAC can prevent contrast nephropathy in diabetic patients with pre-existing renal insufficiency after cardiac angiography. Our study differs from previous studies [21-24,31] in that our study population was a homogeneous group of patients who were at especially high risk of RCIN because of the coexistence of diabetes and renal insufficiency. Because only diabetic patients with pre-existing renal insufficiency were enrolled, and all the patients received the same kind of radiocontrast agent after adequate hydration, the difference in the incidence of RCIN is related directly to the prophylactic use of NAC. However, due to strict inclusion and exclusion criteria and availability of newer iso-osmolar contrast medium, Visipaque, our study was forced to be terminated early and only 20 out of 2846 patients enrolled completed the study. Compared with previous studies, the inclusion criteria for chronic renal insufficiency is defined as a creatinine plasma level ≥ 1.2 mg/dL (and/or clearance < 50 mL/min) by Tepel et al [21], a creatinine plasma level ≥ 1.2 mg/dL (and/or clearance < 60 mL/min) by Kay et al [23], and a creatinine plasma level ≥ 1.4 mg/dL (and/or clearance < 40 mL/min) in the APART trial [31]. It is likely that some enrolled patients had normal or near normal renal function in their studies; hence, we set higher inclusion criteria.

As recommended in earlier studies, we defined an acute radiocontrast-induced nephropathy as a 25% rise from baseline or an absolute increase of 0.5 mg/dL in SCC after angiography. To exclude the possibility that the effects of acetylcysteine were only due to a direct effect on the tubular secretion of creatinine, with renal function left unaffected, we also measured serum urea nitrogen. The changes in serum urea nitrogen concentrations were similar to those in SCC, suggesting that changes in glomerular filtration may underlie the observed changes in SCC. Furthermore, for feasibility of comparison, we administered NAC in the same manner as that reported by Tepel et al [21].

In our study, the changes in SCC and CCR among different stages were insignificant in both groups. Theoretically, the changes in SCC cannot represent the changes of renal function because there is no linear relationship between SCC and renal function. The differences between CCR can more accurately reflect the changes in glomerular filtration rate; hence, the comparison is more reliable using CCR as an outcome parameter. After angiography, CCR increased in the NAC group at day 2 and returned to the prior level at day 5. In the control group, CCR did not change significantly after angiography at days 2 and 5. Interestingly, after contrast agent use, glomerular filtration rate increased after treatment with NAC and returned to baseline level after discontinuation of the drug. The changes would be significant if sample size were large enough. Though the changes in SCC and CCR among different stages are insignificant in both groups, the clinical outcomes are promising. None of the patients in the NAC group developed RCIN and five patients in the control group experienced RCIN 5 days after angiography. The rate of RCIN is lower in the NAC group (0% *vs* 56%, $p = 0.006$, N = 20). The average length of hospitalization is shorter in the NAC group (5.2 *vs* 8.1 days, $p = 0.04$, N = 20). Based on our findings, NAC seems to be effective for the prevention of RCIN after cardiac angiography in diabetic patients with nephropathy.

The pathogenesis of RCIN is not completely understood. There is some evidence that either renal vasoconstriction and/or tubular toxic damage caused by oxidant stress may play a role. Contrast infusion causes a brief increase in

renal plasma flow and glomerular infiltration rate, followed by sustained decrease in both parameters due to release of vasoactive mediators (such as endothelin) in the kidney. An animal study suggests that NAC has vasodilatory properties [32]. However, a correlation between renal vasoconstriction and the development of renal failure has not been found in humans [33]. On the other hand, through measurement of oxidative stress before and after NAC use in patients with chronic renal insufficiency undergoing coronary angiography, Drager LF et al found that renal function improved and oxidant stress-mediated proximal tubular injury was suppressed [34].

However, suppression of oxidant stress mediated by NAC can only explain the prevention of contrast nephropathy rather than the improvement of renal function. Recent studies found that both oxidative stress and inflammation may contribute to chronic renal disease pathophysiology [35]. We hypothesize that the oxidant stress causing chronic renal disease would be ameliorated by NAC, reflecting an increase in CCR. After angiography, the reactive oxygen species (ROS) generated by contrast medium and pre-existing ROS would decrease due to correction of redox imbalance via NAC or its metabolites thereby protecting proximal renal tubule cells. After discontinuation of NAC administration, production of ROS would increase and CCR wound begin to decrease and return to prior levels, as demonstrated in our study. The way to prove this is to design a study to assess the changes in urine free radical amounts in patients with chronic renal insufficiency receiving NAC. Furthermore, orally administered NAC leads to peak serum levels in approximately one hour, and the elimination half life is 2.1 hours [36]. The doses and intervals of administration of NAC proposed by previous researchers should be challenged.

Our study was terminated early because of the availability of a new non-ionic iso-osmolar contrast medium, Visipaque, which is less nephrotoxic than the non-ionic low-osmolar contrast medium, Omnipaque [27]. Since Omnipaque is more nephrotoxic than Visipaque, such studies should not be conducted with Omnipaque again in the future in patients with renal insufficiency. Several meta-analyses [31,37,38] suggest that a larger sized population should be surveyed; however, we believe that the key point to clarify the underlying mechanism of NAC and whether it can prevent contrast nephropathy lies in the design of the study, including measurement of urinary oxidative stress, doses, intervals and duration of NAC administration rather than the size of the population.

Our study has several limitations. For example, the results are from a single institution, and sample sizes are small, although adequately powered. Also, the study was terminated early because of ethical concerns. Furthermore, more patients had a history of stroke in the control group than in the study group. It was anticipated that the incidence of renal atherosclerosis would be higher, which would impair renal perfusion. However, abdominal aortography did not disclose renal artery stenosis in either group. Finally, all of our patients continued ACEi and ARB during the study. Data on the use of ACEi and the associated risks for RCIN are sparse and conflicting [39-41]. In some studies, ACEi has been identified as a risk factor for RCIN because of its potential to reduce renal function [39,42]. Under normal conditions, ACEi is not nephrotoxic. Rather, it alters the hemodynamics within the glomerulus [43]. Nevertheless, it is a common practice in many centers to hold ACEi before contrast administration. In our study, more patients in the control group received ACEi which might have altered renal perfusion and influenced the results of our study.

In conclusion, NAC is effective for the prevention of iohexol-related RCIN after cardiac angiography in diabetic patients with nephropathy.

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心臟血管攝影術前對糖尿病合併慢性腎功能不全患者給予N-乙醯半胱胺酸來預防顯影劑所造成的腎病變

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目的　針對均質的高危險病患群，我們設計了一項實驗來確定N-乙醯半胱胺酸對於預防顯影劑造成之腎病變到底有沒有影響。

方法　這是一個隨機、單盲、安慰劑控制的前瞻性臨床研究。包含適合之糖尿病合併慢性腎功能不全的患者(肌酐酸濃度大於1.6 mg/dL或肌酐酸廓清率小於40 mL/min)，他們都是接受冠狀動脈攝影或介入性治療的患者，同時使用了大量之低分子量，非離子性顯影劑(iohexol，劑量大於每公斤體重1.5 mL)。所有的病患在術前均接受0.45%生理食鹽水靜脈注射(每公斤體重每小時1 mL，由術前12小時起，至術後12小時止)。A組的病患使用N-乙醯半胱胺酸(一日兩次，每次600 mg，共4次，由術前一天開始)。B組的病患則給予安慰劑(一日兩次，共4次，由術前一天開始)。在開始接受心導管術前，心導管術後第2天，以及術後第5天各測一次肌酐酸的濃度。顯影劑造成之腎病變是定義爲術後之肌酐酸濃度上升25%，或是絕對值上升0.5 mg/dL。主要的研究結果是顯影劑造成之腎病變的危險性，並採用足夠解釋小樣本差異之非母數統計分析結果。

結果　有20位病患完成本試驗。在N-乙醯半胱胺酸組與控制組中，兩組在年齡、性別、體重、血壓、進行心臟血管攝影術之時間、使用的顯影劑量方面均無顯著差異。在心臟血管攝影術兩天後，肌酐酸廓清率在兩組無明顯變化(N-乙醯半胱胺酸組24.5 ± 10.3 *vs* 29.6 ± 10.6 mL/min，N = 11，p = 0.34；控制組27.4 ± 10.3 *vs* 29.6 ± 10.6 mL/min，N = 9，p = 0.57)；而在五天後與術前比較，肌酐酸廓清率在兩組皆無顯著差異(N-乙醯半胱胺酸組24.5 ± 10.3 *vs* 27.4 ± 11.8 mL/min，N = 11，p = 0.40；控制組27.4 ± 10.3 *vs* 24.2 ± 8.8 mL/min，N = 9，p = 0.43)。在N-乙醯半胱胺酸組中沒有人發生顯影劑造成之腎病變；而在控制組中有五人發生顯影劑造成之腎病變。N-乙醯半胱胺酸組在顯影劑造成腎病變發生率上較低(0% *vs* 56%，p = 0.006，N = 20)，且平均住院日較短(5.2 *vs* 8.1 天，p = 0.04，N = 20)。在本試驗中，並沒有病患因發生顯影劑造成之腎病變而須接受透析治療。

結論　在糖尿病患者合併慢性腎功能不全之病患進行心臟血管攝影術前給予N-乙醯半胱胺酸來預防顯影劑iohexol所造成的腎病變是有效的。（**中台灣醫誌 2007;12:173-83**）

關鍵詞

心臟血管攝影術，乙醯半胱胺酸，顯影劑造成之腎病變

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