Does N-Acetylcysteine Reduce the Incidence of Contrast-Induced Nephropathy and Clinical Events in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction?

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Abstract

Objectives We examined oral N-acetylcysteine effects on contrast-induced nephropathy (CIN) and clinical events in patients undergoing primary angioplasty for acute myocardial infarction.

Background Recent studies have reported that N-acetylcysteine reduces CIN and improves the clinical outcome in patients undergoing primary angioplasty. However, additional investigations are warranted to further support these findings.

Methods We randomly assigned 76 patients undergoing primary angioplasty into two groups: 38 patients were assigned to N-acetylcysteine (NAC, 705 mg orally administration before and 12, 24, 36 hours after primary angioplasty), and 38 patients to placebo. CIN was defined as an increase in the serum creatinine concentration of 25 percent or more from baseline value within the 72-hour period after primary angioplasty.

Results CIN occurred in 7 patients (9.2%). In the NAC group, the incidence of CIN tended to be lower than in the placebo group (NAC; 2/38; 5.3% vs. Placebo; 5/38; 13.2%, $p=0.21$). The composite endpoints such as death, acute renal failure requiring temporary renal replacement therapy, or need for mechanical ventilation did not occur in either group.

Conclusion While N-acetylcysteine might have the possibility to reduce the incidence of contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction, the in-hospital mortality and morbidity were not significantly different between the two groups.

Key words: N-acetylcysteine, contrast-induced nephropathy, primary angioplasty

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Introduction

Contrast induced nephropathy (CIN) is one of the major complications of coronary intervention and has been postulated to be correlated with mortality (1, 2). This is especially important for patients treated with primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) where the incidence of CIN has been shown to be higher (3). Thus, there is significant clinical interest in the prevention of CIN in PCI patients.

Tepel et al reported that prophylactic administration of the

antioxidant N-acetylcysteine (NAC) prevented renal damage in patients undergoing contrast-enhanced computed tomography (4). While numerous trials have been conducted in coronary angiography and PCI, the effect of NAC in the prevention of CIN remains controversial.

Recently, several meta-analyses of randomized controlled trials reported the effectiveness of NAC for preventing CIN (5-8). However, most previous trials evaluated only the occurrence of CIN as the endpoint and it was unclear whether those findings were associated with clinical outcomes. One study demonstrated that patients receiving NAC experienced shorter hospital stays and thus lower cost as

endpoints (9). On the other hand, Miner et al reported that NAC reduced CIN but did not affect the clinical event rate during long term follow-up (10).

Marenzi et al reported that NAC not only reduced CIN but improved in-hospital clinical outcomes in patients undergoing primary angioplasty and they suspected an extrarenal effect or contribution (11). However, to further support NAC administration to avert the incidence of CIN, we chose to investigate the effect of NAC through a prospective, randomized trial in patients undergoing primary angioplasty for acute myocardial infarction (AMI).

Methods

Study population

Between August 2007 and September 2008, 82 consecutive patients admitted for ST-segment elevation acute myocardial infarction (STEMI) treated with primary PCI at Okazaki City Hospital were enrolled. Exclusion criteria included dialysis, known allergy to NAC, and inability to take NAC orally. The study was approved by the ethics committee of our institution and all patients gave written informed consent.

Study protocol

After enrollment, patients were randomly assigned to two groups (NAC group, placebo group). Patients in the NAC group received 705 mg NAC (Mucofilin[®], 352.4 mg N-acetylcysteine per 2 milliliter, Eisai, Japan) orally before and 12, 24, 36 hours after intervention (Total 2,820 mg). Patients in the placebo group received 4 milliliters of water instead.

All patients received hydration with intravenous Ringer's lactate solution at a rate of 1-2 mL/kg/hr for more than 12 hours after primary angioplasty. Based on patient needs, the attending physicians were permitted to prescribe the use of beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, diuretics, inotropic drugs and intraaortic balloon pump (IABP) as indicated. We gave IABP for the cases with symptomatic heart failure, cardiac shock, low left ventricular function, multi-vessel disease, or proximal occlusion of the left anterior descending artery.

Initial echocardiographic evaluations were performed in all patients within 24 hours of admission by expert sonographers. Serum creatinine levels were measured just before primary angioplasty, and then every day for the following three days. Creatinine clearance (CCr) was calculated by applying the Cock-Croft-Gault formula : $CCr \text{ (mL/min)} = [(140 - \text{age}) \times \text{weight (kg)}] / [\text{serum Cr (mg/dL)} \times 72]$, corrected in women by a factor of 0.85 (12). Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study Group equation (13).

In this study, hypertension was defined as a diagnosed history of hypertension or requiring anti-hypertensive drugs. The definition of dyslipidemia was that the patient had re-

ceived lipid lowering medications or the blood exam on admission showed a serum LDL-cholesterol level of 140 mg/dL or above, serum triglyceride level of 150 mg/dL or above, or serum HDL-cholesterol level of 39 mg/dL or lower. Diabetes was defined as a diagnosed history, the fasting plasma glucose level of 126 mg/dL or above, the random plasma glucose level of 200 mg/dL or higher, or HbA1c level of 6.5% or above.

The primary endpoint of the study was the occurrence of CIN was defined as an increase in the serum creatinine level of 25 percent or more from the baseline value within 72 hours after primary angioplasty.

All adverse clinical events were recorded during hospitalization.

Primary angioplasty

Primary angioplasty was performed according to the standard techniques. The choice of arterial access site, guide catheters, balloons and stents was dependent upon the individual physician operator. Patients received an intravenous bolus of 5,000 U heparin in the emergency room followed by an additional bolus and continuous heparin administration to maintain the activated clotting time to more than 300 seconds. A non-ionic, low-osmolality contrast agent, iopamidol (Iopamiron[®], 755 mg iopamidol per milliliter, Bayer, Japan) was used for all procedures in all study patients. All patients were given oral aspirin daily (100 mg) and ticlopidine (200 mg).

Statistical analysis

Continuous data are reported as the mean value $\pm$ SD. Categorical data are presented as absolute values and percentages. Comparison of continuous variables was performed by Student's t test for categorical variables. A p value <0.05 was considered statistically significant. Analysis was conducted with Statcel2 software.

Results

Patient characteristics

A total of 82 patients were initially enrolled. Six were excluded after randomization due to diagnosis of variant angina pectoris, two for unstable angina, two for takotsubo cardiomyopathy, and one who did not receive an intervention. As a result, 76 patients were available for analysis in this study (NAC group; n=38, placebo group; n=38).

Table 1 and 2 show the baseline characteristics of patients in both groups. No significant differences were seen in age, coronary risk factors, history of coronary artery disease, LVEF, peak CK, or volume of contrast between the two groups. Renal function in the placebo group tended to be better, and the rate of IABP use was higher in the placebo group yet statistical differences were not seen.

Incidence of CIN

CIN occurred in 7 patients (7/76: 9.2%). The incidence of CIN in the NAC group tended to be lower than in the placebo group (NAC; 2/38: 5.3% vs. placebo; 5/38: 13.2%, $p=0.21$) (Fig. 1).

No patient experienced an absolute rise in serum creatinine (≥ 0.5 mg per deciliter) within the 72-hour evaluation period in either group.

There was no significant difference regarding renal function (eGFR, serum Cr level) at baseline between patients with CIN ($n=7$) and without CIN ($n=69$), and the incidence of CIN was not related to the presence of impaired renal function (data not shown).

In-hospital clinical outcomes

No major adverse events (death, ARF requiring temporary replacement therapy, need for mechanical ventilation) occurred in either group during the in-hospital follow-up period (Table 3). The incidence of symptomatic congestive heart failure was not significantly different between the two groups (NAC 4/38 vs. placebo 7/38, respectively, ns). Similarly, the duration of hospital stay between the two groups was not statistically different. While one patient in the NAC group vomited after NAC administered, no other significant adverse effects occurred.

Discussion

The aim of this study was to evaluate the effect of oral NAC on CIN and clinical events in STEMI patients undergoing primary angioplasty. This study demonstrated that oral NAC tended to reduce CIN without major negative clinical outcomes in any patients enrolled in this study.

Several meta-analyses have shown that NAC is an effective agent to prevent CIN, especially in patients with chronic renal insufficiency (5-8). With regard to STEMI patients undergoing primary angioplasty, Marenzi et al reported that CIN occurred in 33% of control group, 15% of standard dose NAC group, and 8% of high dose NAC group (11), and another group reported that CIN (defined as a rise in Cr ≥ 0.5 mg/dL) occurred in 19% (3). In the present study, CIN occurred in only 5.3% of the NAC group and 13.2% of

Table 1. Baseline Patient Characteristics (1)

	NAC group	Placebo group	p value
Patients	$n=38$	$n=38$	
Age, yrs	62.8 ± 13	60.5 ± 14	0.47
Male gender	31 (82%)	31 (82%)	1.0
Diabetes	11 (29%)	11 (29%)	1.0
Hypertension	19 (50%)	17 (45%)	0.65
Dyslipidemia	24 (63%)	19 (50%)	0.25
Smoking	14 (42%)	9 (24%)	0.09
OMI	2 (5%)	5 (13%)	0.22
Prior PCI	1 (3%)	4 (11%)	0.18
Prior CABG	0 (0%)	0 (0%)	

OMI, old myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 2. Baseline Patient Characteristics (2)

	NAC group	Placebo group	p value
BMI (kg/m ²)	23.4 ± 3.9	23.8 ± 3.5	0.61
HbA1c (%)	6.3 ± 1.6	6.3 ± 1.8	0.90
Serum Cr (mg/dL)	0.88 ± 0.25	0.80 ± 0.19	0.10
CCr (mL/min) (Cockcroft & Gault)	78 ± 34	91 ± 36	0.12
eGFR (mL/min/1.73m ²)	70 ± 18	77 ± 18	0.07
Cystatin C (mg/L)	0.95 ± 0.34	0.88 ± 0.19	0.25
CKD stage III	13 (34%)	8 (21%)	0.20
CKD stage IV	0	0	
Killip classification $\geq$ II	0	0	
LVEF (%)	53 ± 8.8	52 ± 7.1	0.47
Anterior infarction, n (%)	18 (47%)	17 (45%)	0.82
Peak CK (IU/L)	2384 ± 1863	2900 ± 1850	0.23
IABP, n (%)	10 (26%)	17 (45%)	0.09
Volume of contrast medium (mL)	205 ± 80	216 ± 85	0.54
Volume of contrast medium $\geq$ 300mL, n (%)	5 (13%)	8 (21%)	0.27
Approach site, Radial/Femoral, n	10/28	17/21	0.09
Catheter size, 6Fr/7Fr/8Fr, n	18/13/7	23/12/3	0.32
Stent use, n (%)	38 (100%)	34 (89%)	0.06
Carperitide, n (%)	9 (24%)	9 (24%)	1.0
Catecholamine, n (%)	4 (11%)	5 (13%)	0.5
statin, n (%)	38 (100%)	38 (100%)	
ACEI/ARB, n (%)	32 (84%)	36 (95%)	0.13
Nicorandil, n (%)	34 (89%)	36 (95%)	0.34
Calcium-channel blocker, n(%)	6 (16%)	1 (3%)	0.05
Beta-blocker, n (%)	26 (68%)	19 (50%)	0.10

BMI, body mass index; CCr, creatinine clearance; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; IABP, intraaortic balloon pump; ACEI, angiotension-converting enzyme inhibitor; ARB, angiotension receptor II blocker; NAC, N-acetylcysteine

placebo, and no patient had an absolute rise in Cr (≥ 0.5 mg/dL); thus, the incidence of CIN in our study was much lower in both groups compared with previous studies. We believe that these results may be due to the use of a smaller volume of contrast medium combined with additional hydration. In general, we administered 1,000 mL of intravenous Ringer's lactate solution in the first hour during PCI except in patients with heart failure, followed by a rate of 1-2 mL/kg/hr for more than 12 hours after primary angioplasty. Although renal function at baseline in the NAC group tended to be worse, fewer patients with CIN were observed. This fact suggests the possibility of efficacy of oral NAC for the prevention of CIN in STEMI patients undergoing PCI.

Several prior studies identified CKD, age, diabetes mellitus, anemia, congestive heart failure, hypotension, contrast media volume and IABP as risk factors for the occurrence of CIN (1, 2, 14, 15). When these characteristics were compared between the CIN group (n=7) and non CIN group (n=69), we found that the mean peak CK level in the CIN group was significantly higher ($4,504 \pm 2,409$ vs $2,453 \pm 1,709$ IU/L, $p=0.02$), suggesting that severe patients were more likely to develop CIN. No statistical differences were seen when other factors such as age, diabetes, history of PCI, CABG, renal function at baseline, volume of contrast media, volume of hydration, and the use of IABP were examined. However, the CIN group in our study was a small sample and thus was limited in generalizability for larger patient populations.

Most of the previous studies on NAC evaluated the end-

Figure 1. Incidence of contrast-induced nephropathy (CIN). The incidence of CIN in the N-acetylcysteine (NAC) group tended to be lower than in the placebo group, but statistical difference was not seen.

point of CIN as the primary outcome and had insufficient data of clinical outcomes. Marenzi et al first reported that NAC is significantly effective for the reduction of in-hospital mortality and morbidity. In comparison, the present study had fewer events. In Japan, administration of NAC is limited to the oral type of NAC. As a result, severe patients in cardiogenic shock or respiratory failure who were unable to take NAC orally before the intervention were excluded, which is most unfortunate, as these patients are more likely to develop CIN. This explanation may be one of the reasons for fewer events in our study cohort. However, even allowing for those patients, the in-hospital mortality and morbidity was lower in our study than in other studies.

Several prior studies have examined the dose-dependent effect of NAC on CIN (11, 16). Marenzi et al (11) reported that a single dose of 1200 mg was more effective than 600 mg. In the present study, patients received a single dose of 705 mg. It was difficult to administer oral NAC to AMI patients before PCI because they often had various severe symptoms accompanying their chest pain, such as nausea, and NAC has a distinct odor and taste making it a challenge for patients to swallow. Crouch et al reported the benefits of dilution of NAC in a beverage on the smell and taste of oral NAC (17). Applying that effort, we might have been able to administer a higher dose to boost the effects for the patients.

This study has several limitations. First, severe patients whose inability to swallow oral NAC precluded them from enrollment even though they might have been expected to receive more benefit as described above. However, in 5 precluded patients with symptomatic heart failure or cardiac shock except for cardiopulmonary arrest on arrival, CIN did not occur (0/5, 0%). The incidence of CIN in the patients who resulted in cardiopulmonary arrest was extremely high (6/8, 75%). Second, this is single center study and the sample size was small. Third, since the clinical events occurred less frequently in this study, we were unable to assess the effect on clinical outcomes sufficiently. Large, multicenter trials are required to address these issues more definitively.

In conclusion, this study demonstrated that oral NAC can be safely administered and might have a possibility to reduce the incidence of CIN in AMI patients undergoing primary angioplasty.

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

Table 3. Clinical Outcomes

	NAC group	Placebo group	p value
In-hospital death	0	0	
ARF requiring temporary renal replacement therapy	0	0	
Need for mechanical ventilation	0	0	
Hospital stay, days	18.7±5.6	20.8±8.9	0.22
Adverse effect of NAC	1	0	0.5

ARF, acute renal failure; NAC, N-acetylcysteine

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