RESEARCH

Cardiovascular Therapeutics

N-Acetylcysteine in Preventing Contrast-Induced Nephropathy Assessed by Cystatin C

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SUMMARY

Aims: Prophylactic oral N-acetylcysteine (NAC) has been widely used for prevention of contrast-induced nephropathy (CIN). However, clinical studies have not been demonstrating this effect consistently because of evidence that NAC can alter serum creatinine levels without affecting glomerular filtration rate (GFR). We investigated NAC for the prevention of CIN by monitoring creatinine and cystatin C.

Methods: We enrolled 113 patients (49 patients in NAC group and 64 patients in control group) with normal to subnormal GFR who were scheduled for cardiovascular procedures. Patients in NAC group receive acetylcysteine 600 mg twice a day, on the day before and on the day of cardiovascular procedure. All patients received a periprocedural intravenous infusion ("volume expansion") of 1 ml/kg/h with 0.45% saline for 24 h (12 h before and 12 h after exposure to contrast medium). Serum cystatin C and creatinine levels were measured before and at 12, 24, and 48 h after procedure.

Results: The incidence of cystatin C-based CIN was 28.5% (n = 14) in NAC and 23.4% (n = 15) in control group (p = 0.663) and serum creatinine-based CIN was 12.2% (n = 6) in NAC and 17.2% (n = 11) in control group ($P = 0.468$). In this study, oral NAC had no effect on the prevention of CIN in patients undergoing cardiovascular procedures.

Conclusion: In this study, oral NAC administration does not reduce neither the incidence of cystatin C-based CIN nor serum creatinine-based CIN in patients undergoing cardiovascular procedures.

Introduction

Continuous growth in diagnostic and interventional procedures requires the use of radiographic contrast agents, which has led to a parallel increase in the incidence of contrast-induced nephropathy (CIN). CIN is third, the most common cause of hospital acquired renal failure [1]. Most commonly, it is defined as a change in serum creatinine over baseline by 48 h, such as ≥25% above baseline or an absolute increase in the serum creatinine level of at least 0.5 mg/dL [2]. Early studies showed that preexisting renal impairment, age, anemia, diabetes, congestive heart failure, shock, contrast volume, and osmolality were risk markers for the development of acute deterioration in renal function after contrast medium (CM) administration [3,4].

Although the pathogenesis of CIN in humans is not clear, it is known that reactive oxygen species and renal ischemia play a role in its development [5,6]. N-acetylcysteine (NAC) has the potential to reduce the nephrotoxicity of CMs through antioxidant and vasodilatory effects [7]. Despite the large number of available data, the true benefit of NAC is still unclear [8–10].

Glomerular filtration rate (GFR) is the accepted method for detecting changes of renal function in patients receiving CM. As a breakdown product of muscle, however, serum creatinine concentration is influenced by a variety of nonrenal factors, including age, gender, body weight, and protein intake. Furthermore, creatinine is insensitive for detecting reductions in kidney function, which may deteriorate more than 50% before serum creatinine exceeds the normal range [11,12].

Serum cystatin C concentration, a new endogenous marker of renal function, is believed to be superior to plasma creatinine concentration as an indicator of renal function [13–15]. Cystatin C is a low molecular weight (13 kDa) protein with 120 amino

acids that functions as cysteine protease inhibitor. The protein is freely filtered through the glomerulus and almost completely reabsorbed and catabolized by tubular cells has been proposed as a simple, reliable, and accurate marker of GFR [16]. Thus, the serum concentration of cystatin C—in contrast with plasma creatinine concentrations—does not depend on age, sex, and muscle mass [17,18].

Materials and Methods

Study Population

Patients with normal to subnormal GFR and older than 18 years of age, who were scheduled for elective cardiovascular procedures, were eligible for this study. The exclusion criteria were accepted as patients with uncontrolled hypertension, serum creatinine levels of more than 7 mg/dL, severe valvular heart disease, preexisting dialysis, autoimmune disease, chronic or acute infectious disease, emergency catheterization, recent exposure to radiographic contrast within 10 days, medication with NSAID or metformin up to 3 days before entering study, allergy to radiographic contrast or NAC.

The institutional ethics committee approved the study. Informed consent was obtained from each subject included to the study.

Study Treatment

The patients were assigned to either the acetylcysteine group (NAC group, n = 49) or the control group (n = 64). Patients in NAC group receive acetylcysteine 600 mg twice a day, on the day before and on the day of cardiovascular procedure. All patients received a periprocedural intravenous infusion ("volume expansion") of 1 mL/kg/h with 0.45% saline for 24 h (12 h before and 12 h after exposure to CM). Estimated GFR was calculated by applying the level-modified Modification of Diet in Renal Disease (MDRD) formula: (186.3 × serum creatinine –1.154) × (age–0.203) × (0.742 if female) [19]. Serum cystatin C and creatinine levels were measured before and at 12, 24, and 48 h after procedure. Serum creatinine was measured by the standard laboratory method. Serum cystatin C was determined by sandwich enzyme immunoassay using a kit (Abnova, Taiwan). Hemoglobin, fasting glucose, blood pressure, ejection fraction, and carotid intima media thickness (c-IMT) were studied on admission. We also estimated Mehran risk score, reflecting the risk of contrast nephropathy before the procedure. Mehran risk score is calculated according to several risk factors, including dose of contrast media, baseline creatinine clearance, older age, hypotension, heart failure, anemia, and diabetes, as well as the use of intra-aortic balloon pump [4].

Cardiovascular Procedures

The performance of angiography, ventriculography, angioplasty, and coincident noncoronary angiography was left to the discretion of the cardiologist. Cardiologists performing cardiovascular procedures were blinded to the group assignments. A nonionic low-osmolar contrast agent (Iomeron® 350 [350 mg iodine/ mL] Bracco S.p.A ve Patheon ITALIA S.p.A., Italy) containing iomeprol was used in all patients.

Study Purpose

The primary purposes of the study were (1) to assess a reduction in the incidence of cystatin C-based CIN in the acetylcysteine group, as compared with the control group and (2) to assess whether early changes in cystatin levels anticipate the occurrence of CIN. Serum cystatin C-based CIN was defined as an increase in the serum cystatin C concentration greater than 25% within 48 h of contrast exposure. Serum creatinine-based CIN was defined as an increase in serum creatinine concentration greater than 25% within 48 h of contrast exposure. In studies in which creatinine and cystatin C concentrations were compared, the same percentage change in concentrations of both markers was considered representative of a significant decrease in renal function [17].

Statistical Analysis

The data are expressed as mean ± standard deviation for continuous variables and as frequency (number [%]) for categorical variables. Mean, standard deviation, 25, median (50), and 75 percentiles of the continuous variables were given. The normality of data distribution was tested with the Shapiro–Wilk and Kolmogorov–Smirnov tests. The Student *t*-test and Mann–Whitney U test were used to determine differences between mean values for normally and nonnormally distributed variables, respectively. χ^2 test was used for the comparison of categorical variables. The repeated measures of ANOVA test was done to assess the serial changes of serum cystatin C and creatinine concentration. ROC analysis was used to test predict opaque nephropathy according to the changes in serum cystatin C after contrast exposure. Data were analyzed using SPSS for Windows, version 15 (Chicago, IL, USA), and P values <0.05 were considered statistically significant.

Results

We compared 49 patients receiving NAC with 64 patients in control group. The mean age of study population was 61.6 ± 9.6 years old and men were 75 (66.4%) patients. The prevalence of diabetes was 24.8%.

Of the 113 procedures, 96 were diagnostic angiographies and 17 were interventional procedures. Characteristics for the study patients are shown in Table 1. The two groups of patients were similar for age, sex, body mass index, systolic BP, diastolic BP, diabetes, baseline renal function tests (creatinine, estimated GFR-MDRD, and cystatin C), and Mehran risk score. The volume of contrast was not significantly different between the groups.

Baseline and post procedural 12, 24, and 48 h creatinin and cystatin C levels are shown in Table 2.

There was no difference between two groups in regard of baseline and postprocedural creatinine and cystatin levels.

The overall incidence of cystatin C-based CIN among all study subjects was 25.6% (28.5% in NAC group and 23.4% in control

Table 1 Baseline characteristics of the study subjects

	NAC (n = 49)	Control group (n = 64)	*P* value
Age (years)	62.73 ± 9.62	60.84 ± 9.54	NS
Men (%)	67.3	65.6	NS
Systolic BP (mm Hg)	130.33 ± 18.86	130.23 ± 19.13	NS
Diastolic BP (mm Hg)	79.69 ± 10.46	77.58 ± 10.19	NS
DM (%)	22.4	26.5	NS
BMI (kg/m^2)	27.41 ± 4.15	28.12 ± 3.93	NS
Volume of contrast agent (mL)	81.73 ± 48.82	97.89 ± 80.91	NS
Volume of contrast agent/BMI	3.06 ± 1.93	3.52 ± 3.18	NS
Mehran risk score	2.63 ± 2.47	2.46 ± 2.16	NS
Hemoglobin (g/dL)	13.26 ± 1.49	13.51 ± 1.73	NS
GFR (MDRD) (mL/min)	78.31 ± 20.56	83.56 ± 18.72	NS
LVEF (%)	51.79 ± 8.51	51.33 ± 10.21	NS
cIMT (mm)	1.04 ± 0.13	1.04 ± 0.12	NS

Data are expressed as mean ± SD and parenthesis number means percentage.
Abbrevations: DM, diabetes mellitus; BMI, body mass index; LVEF, left ventricular ejection fraction; GFR (MDRD), glomerular filtration rate (Modification of Diet in Renal Disease); cIMT, carotid intima media thickness.

Table 2 Serial changes of creatinine and cystatin in each group

	NAC (n = 49)	Control group (n = 64)	*P* value
Baseline creatinine (mg/dL)	0.91 ± 0.25	0.83 ± 0.17	NS
Creatinine at 12 h (mg/dL)	0.92 ± 0,27	0.84 ± 0.17	NS
Creatinine at 24 h (mg/dL)	1.01 ± 0.33	0.91 ± 0.19	NS
Creatinine at 48 h (mg/dL)	0.99 ± 0.33	0.92 ± 0.18	NS
Baseline cystatin C (ng/ml)	1425.89 ± 344.84	1449.51 ± 468.34	NS
Cystatin at 12 h (ng/ml)	1432.05 ± 482.45	1490.88 ± 618.91	NS
Cystatin at 24 h (ng/mL)	1547.91 ± 531.07	1506.65 ± 423.43	NS
Cystatin at 48 h (ng/mL)	1699.61 ± 521.67	1548.73 ± 475.36	NS

group, $P = 0.663$) and that of serum creatinine-based CIN was 15.0% (12.2% in NAC group and 17.2% in control group, $P = 0.468$). No patient with development of CIN required dialysis. There was no adverse effect related to NAC treatment.

GFR was calculated according to their serum creatinin and cystatin value at baseline, 12, 24, and 48 h after intervention. Cokcroft–Gault (CG) and HOEK formula were used for GFR estimation. Repetitive values for GFR were tested with ANOVA for each time series. The important finding revealed from the ANOVA test is early decline in serum cystatin at 12 and 24 h imply with the later creatinine increase at 48 h. In addition supports the finding is patients with CIN had greater decrease in serum cystatin at first 12 h compared to the baseline. The other analysis was done according to their postprocedural serum creatinin value. Patients classified according to their creatinin increase after intravenous opaque administration as 15%, 25%, 35%, and 45% regardless from their cysteine value (Figure 1A–D). More prominent creatinin increase can be predictable with early cystatin decrease. Patient with lower serum cystatin levels compared to the baseline at 12 and 24 h have higher incidence of CIN at 48th hours. There was a correlation between cystatin value at 12 and 24th hour's ($r = 0.384$, *P*: 0.0001). Fifteen percent or more creatinin increase can be predictable with cystatin decrease $r = -0.341$, *P*: 0.006 (Figure 1A–D). More than 15% increase in creatinin value is predictable with 39% decrease in cystatin serum value at 12 h, compared to baseline with 94% sensitivity (AUC 0.352; 0.013) in the ROC analysis (Figure 2).

Discussion

Our study shows that orally NAC administration does not reduce neither the incidence of cystatin C-based CIN nor serum creatinine-based CIN in patients undergoing cardiovascular procedures.

CIN, a major cause of hospital-acquired renal failure, is associated with prolonged hospitalization and increased morbidity and mortality [20]. Among all procedures utilizing CM for diagnostic or therapeutic purposes, cardiovascular procedures are associated with the highest rates of CIN [21]. CIN has been reported to occur in 11–44% of patients with moderate renal insufficiency [1]. Risk factors for CIN include preexisting renal failure (especially diabetic nephropathy and multiple myeloma), hypovolemia, administration of (cumulative) high doses of (hyperosmolar) contrast media, and concomitant use of nephrotoxic drugs [22,23].

Although serum creatinine is widely used as such a marker, it should be kept in mind that it is influenced by age, gender, muscle mass, and protein intake, and that it shows low sensitivity for the

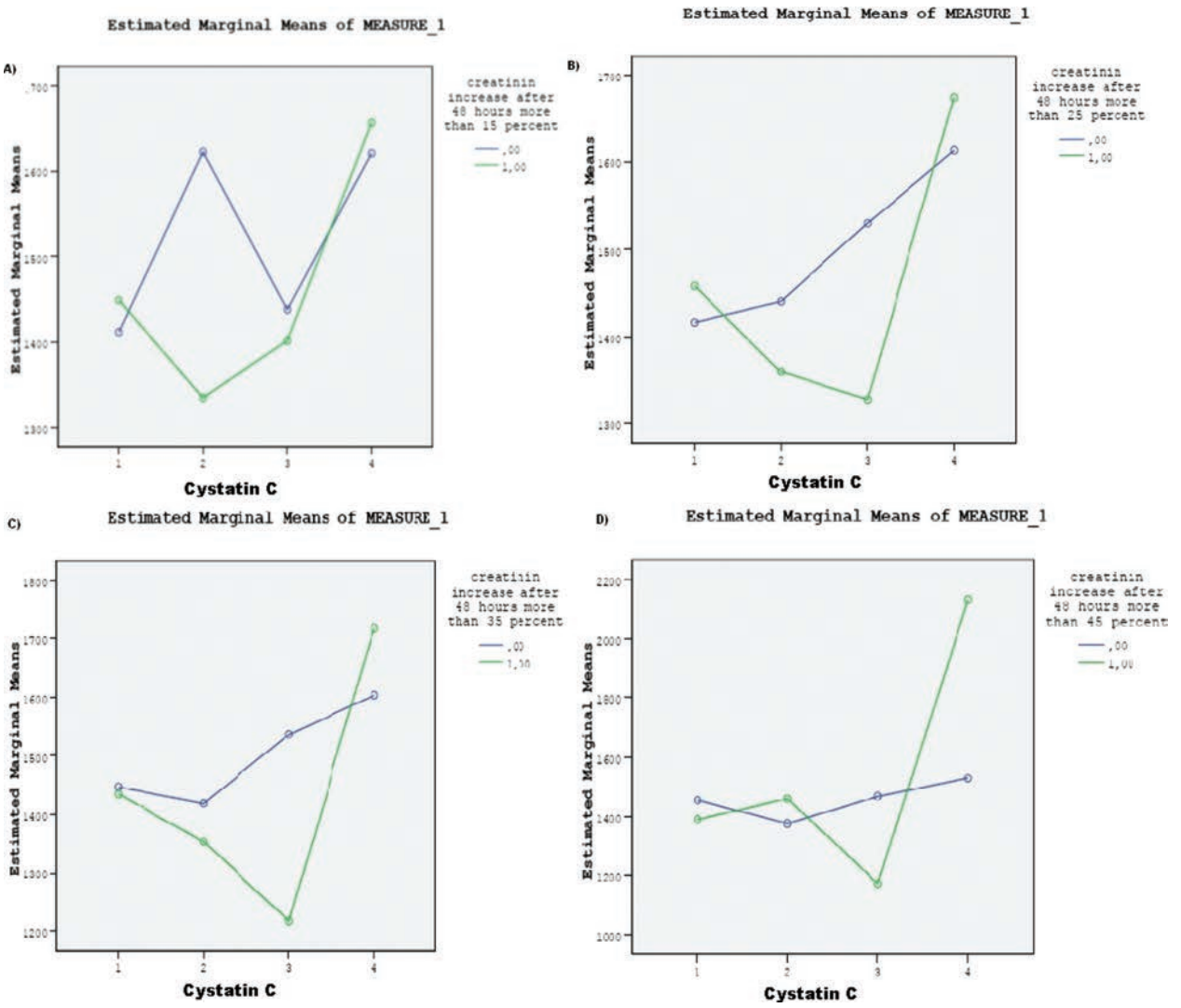

Figure 1 (A) The repeated measures of ANOVA test. Cystatin levels at baseline, 12, 24, and 48 h are shown with 1, 2, 3, 4 in patients with or without creatinine increased more than 15%. Creatinine level increased more than 15% at 48 h is shown with blue color and creatinine clearance increased more than 15% is shown with green color. (B) The repeated measures of ANOVA test. Cystatin levels at baseline, 12, 24, and 48 h are shown with 1, 2, 3, 4 in patients with or without creatinine increased more than 25%. Creatinine clearance increased more than 25% is shown with green color. (C) The repeated measures of ANOVA test. Cystatin levels at baseline, 12, 24, and 48 h are shown with 1, 2, 3, 4 in patients with or without creatinine increased more than 35%. Creatinine clearance increased more than 35% is shown with green color. (D) The repeated measures of ANOVA test. Cystatin levels at baseline, 12, 24, and 48 h are shown with 1, 2, 3, 4 in patients with or without creatinine increased more than 45%. Creatinine clearance increased more than 45% is shown with green color.

detection of early renal dysfunction [24,25]. Cystatin C is a 13 kD endogenous cysteine proteinase inhibitor and is produced by nucleated cells at a constant rate. Cystatin C is freely filtered by the glomerulus, reabsorbed, and catabolized, but it is not secreted by the tubules [26,27]. Many studies have demonstrated the superiority of serum cystatin C for detecting early renal impairment than creatinine and creatinine clearance calculated by the CG formula or the MDRD [27,28].

NAC is the most studied prophylaxis agent to date. The mechanism of action by which it exerts its nephroprotective effects is unknown but it is postulated to act as a free-radical scavenger. In an initial trial, Tepel et al. demonstrated protective effect of NAC (600 mg twice daily on the day before and the day of the scan) in CIN [5]. Since that seminal study there have been many published studies with great heterogeneity in results, some finding substantial benefit for NAC, others reporting no effect. Possible explanations for these contrasting results are differences in applied hydration regimens, in the patient populations studied and in the volumes of contrast media administered, and variations in the timing and dosing of NAC. Also efficacy of NAC is controversial

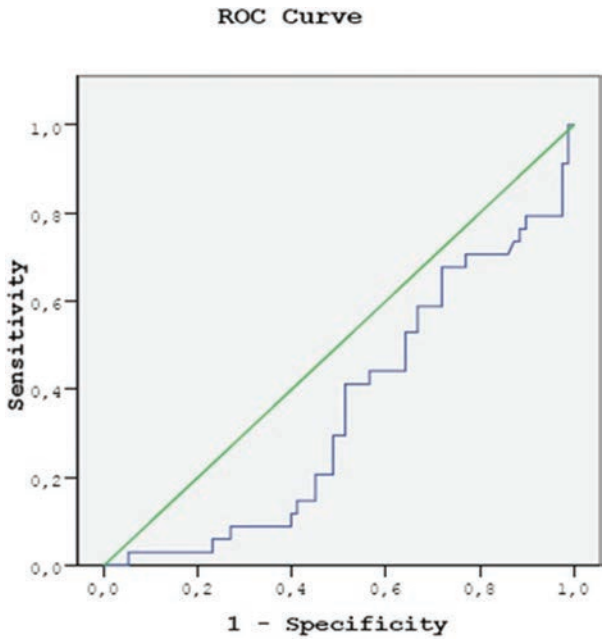

Figure 2. ROC analysis. Sensitivity of relationship between decline in cystatin 0–12 h as a percentage and increase in creatinine more than 15% was calculated AUC 0.352, $P = 0.013$.

because of evidence that NAC can alter serum creatinine levels without affecting GFR. Therefore, cystatin C seems to be more sensitive than creatinine for evaluation of the renoprotective role of NAC after administration of CM. However, there is a little data available on the effect of NAC on the development of cystatin C-based CIN after CM exposure. Poletti et al. randomly assigned 87 patients with renal insufficiency that underwent emergency computed tomography (CT) to NAC and hydration (900 mg injection of NAC 1 h before and another immediately after injection of CM) or only hydration. Average contrast administered was 126 ± 22 mL in NAC group and 125 ± 24 mL in control group. Nine of 43 (21%) patients in the control group and 2 of 44 (5%) patients in NAC group had serum creatinine based CIN ($P = 0.026$). Nine of 40 (22%) patients in the control group and 7 of 41 (17%) patients in NAC group had cystatin-C based CIN ($P = 0.59$). The authors demonstrated renoprotective effect of IV NAC against CIN according to serum creatinine, but did not demonstrate similar effect according to serum cystatin C based CIN [29]. Kim et al. enrolled 166 patients with apparently normal renal function that underwent elective coronary angiography to NAC (oral acetylcysteine at 600 mg twice a day, on the day before and on the day of coronary angiography) or placebo. Average contrast administered was 201 ± 44 mL in NAC group and 216 ± 166 mL in control group. The overall incidence of cystatin C-based CIN among all study subjects was 10.2% (5.0% in NAC group and 15.1% in control group, $P = 0.05$) and that of serum creatinine-based CIN was 6% (3.8% in NAC group and 8.1% in control group, P = NS). These investigators concluded that NAC prevented cystatin based CIN and serum cystatin C more sensitive marker of the early CIN than serum creatinine [30].

Kimmel et al. randomly assigned 54 patients with moderately impaired kidney function to an oral treatment for 2 days with 1.2 g/day of NAC, for 1 day with 60 mg/day of Zn or placebo. Average of CM volumes were 219 ± 105 mL in control group, 187 ± 88 mL in NAC group, and 173 ± 85 mL in Zinc group (P = NS). In this study authors showed that NAC has no effect in preventing CIN by the standard definition, but based on cystatin C they can confirm a preventive effect of NAC [31]. Two of these trials demonstrated preventive effect of NAC based on cystatin C assessment. The volumes of CM in these studies were considerably greater [30,31]. In the study by Kim et al. overall incidence of CIN was lower than in the other two trials. It would be explained by differences in study design. Kim et al. enrolled patients with normal renal function. In the study by Poletti et al. intravenous protocol of NAC was used. In the other two trials oral treatment of 1200 mg NAC was preferred. The dose of oral NAC in our study was similar to previous studies.

The purpose of our study was to evaluate the renoprotective effect of NAC in patients with normal to subnormal function who underwent elective cardiovascular procedures. We first analyzed changes in serum creatinine and cystatin C concentrations in NAC and control groups at baseline, 12, 24, and 48 h after procedure. The overall incidence of cystatin C-based CIN among all study subjects was higher, but not significantly higher, than serum creatinine-based CIN. This is explained as serum cystatin C levels have been reported to be a more sensitive to detect early changes in renal impairment than serum creatinine levels [32,33]. In this study, we observed that early (12 and 24 h) decline in cystatin level predict CIN at 48 h. In our study average of CM volume was 90.8 ± 69.1 mL, because in high-risk patients we avoided left ventriculography. The volume of contrast used in three of the studies was higher than used in our study [31–33]. The administration of fluids is the cornerstone treatment to reduce the risk of CIN. Although the optimal hydration strategy is uncertain, available data support a regimen of 0.9% saline at 1 mL/kg/h intravenously for 12 h before administration of the CM and continuing for up to 12 h after [34]. The hydration protocol used in our study was the same as that used in previous studies (1 mL/kg/h for 12 h before and 12 h after procedure) [30,31].

Our study shows that in patients with normal to subnormal GFR, prophylactic oral NAC administration is ineffective at preventing either cystatin C-based CIN or serum creatinine based CIN development after elective cardiovascular procedures. The inefficacy of NAC therapy may be due to several factors, including the presence of adequate saline infusion, normal renal function, and low opaque volume. The second observation of our study that early decline in cystatin level may predict CIN at 48 h.

Study Limitations

In this study, the patients were observed for only 12–48 h. We cannot exclude the possibility that an earlier change (first 6 h) may occur. Also it is possible that changes in renal function could have occurred after 48 h, and consequently, the measuring of the renal function test within 48 h after the procedure may cause underestimation of the nephropathy risk.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: A prospective controlled study. *N Engl J Med* 1989;**320**:143–149.
2. McCullough PA, Sandberg KR. Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 2003; **4**(Suppl 5):S3–S9.
3. Gupta R, Gurm HS, Bhatt DL, Chew DP, Ellis SG. Renal failure after percutaneous coronary intervention is associated with high mortality. *Catheter Cardiovasc Interv* 2005;**64**:442–448.
4. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. *J Am Coll Cardiol* 2004;**4**:1393–1399.
5. 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* 2000;**343**:180–184.
6. Heyman SN, Clark BA, Kaiser N, et al. Radiocontrast agents induce endothelin release in vivo and in vitro. *J Am Soc Nephrol* 1992;**3**:58–65.
7. Fishbane S, Durham JH, Marzo K, Rudnick M. N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 2004;**15**:251–260.
8. Nallamothu BK, Shojania KG, Saint S, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004;**117**:938–947.
9. Hoffmann U, Fischereder M, Krüger B, Drobnik W, Krämer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. *J Am Soc Nephrol* 2004;**15**:407–410.
10. Marenzi G, Assanelli E, Marana I, et al. N-Acetylcysteine and contrast induced nephropathy in primary angioplasty. *N Engl J Med* 2006;**354**:2773–2782.
11. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem* 1992;**38**:1933–1953.
12. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function– measured and estimated glomerular filtration rate. *N Engl J Med* 2006;**354**:2473–2483.
13. Randers E, Erlandsen EJ. Serum cystatin C as an endogenous marker of the renal function—A review. *Clin Chem Lab Med* 1999;**37**:389–395.
14. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW. Biological variation of cystatin C: Implication for the assessment of glomerular filtration rate. *Clin Chem* 1998;**44**:1535–1539.
15. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO. Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995;**47**:312–318.
16. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez- Bru C, Grubb A. Cystatin C as a marker of GFR history, indications, and future research. *Clin Biochem* 2005;**38**:1–8.
17. Herget-Rosenthal S, Marggraf G, Hüsing J, et al. Early detection of acute renal failure by serum cystatin C. *Kidney Int* 2004;**66**:1115–1122.
18. Julier K, da Silva R, Garcia C et al. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebocontrolled, multicenter study. *Anesthesiology* 2003;**98**:1315–1327.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002;**39**(suppl 1):S1–S237.
20. Rihal C, Textor S, Grill D, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;**105**:2259–2264.
21. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002;**39**:930–936.
22. Rich MW, Crecelius CA. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. *Arch Intern Med* 1990;**150**:1237–1242.
23. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 1994;**45**:259–265.
24. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as filtrationmarker in glomerulopathic patients. *Kidney Int* 1985;**28**:830–836.
25. Perrone RD, Madis NE, Levey AS. Serum creatinine as a index of renal function: New insights into old concepts. *Clin Chem* 1992;**38**:1933–1953.
26. Abrahamson M, Olafsson I, Palsdottir A, et al. Structure and expression of the human cystatin C gene. *Biochem J* 1990;**268**:287–294.
27. Tenstad O, Roald AB, Grubb A, Aukland K. Renal handling of radiolabelled human cystatin C in the rat. *Scand J Clin Lab Invest* 1996;**56**: 409–414.
28. Pucci L, Triscornia S, Lucchesi D, et al. Cystatin C and estimates of renal function: Searching for a better measure of kidney function in diabetic patients. *Clin Chem* 2007;**53**:480–488.
29. Poletti PA, Saudan P, Platon A et al. I.v. N-acetylcysteine and emergency CT: Use of serum creatinine and cystatin C as markers of radiocontrast nephrotoxicity. *AJR Am J Roentgenol* 2007;**189**(3):687–692.
30. Kim BJ, Sung KC, Kim BS, et al. Effect of N-Acetylcysteine on cystatin C-Based renaL function after Elective coronary angiography (ENABLE Study): A prospective, randomized trial. *Int J Cardiol* 2010;**138**(3):239–245.
31. Kimmel M, Butscheid M, Brenner S, Kuhlmann U, Klotz U, Alscher DM. Improved estimation of glomerular filtration rate by serum cystatin C in preventing contrast induced nephropathy by N-acetylcysteine or zinc–preliminary results. *Nephrol Dial Transplant* 2008;**23**:1241–1245.
32. Coll E, Botey A, Alvarez L, et al. Seum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis* 2000;**36**:29–34.
33. Mussap M, Dalla Vestra M, Fioretto P, et al. Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. *Kidney Int* 2002;**61**: 1453–1461.
34. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006;**354**:379–386.