

Article

Comparison of *N*-acetylcysteine and ascorbic acid in prevention of renal dysfunction after coronary angioplasty

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Abstract

Background: Contrast agents can cause a reduction in renal function that may be due to generation of reactive oxygen species. Conflicting evidence suggests that administration of the antioxidant, *N*-acetylcysteine (NAC) prevents this renal impairment. The literature on the protective role of ascorbic acid is scarce.

Objective: To compare the effects of NAC and ascorbic acid monotherapy with placebo in reducing the incidence of contrast-induced nephropathy (CIN) after coronary angioplasty.

Methods: We conducted a randomized, double-blind, placebo-controlled trial of NAC and ascorbic acid monotherapy in 150 patients with any baseline serum creatinine who underwent coronary angioplasty. NAC 600 mg b.i.d. for 2 days, ascorbic acid 1.5 g b.i.d. for 2 days or placebo administered orally with the first dose initiated on the day before the procedure. The primary end point of our study was the incidence of CIN, defined as a relative increase in serum creatinine of at least 25% measured 4 days after the procedure.

Result: CIN occurred in 4 of the 50 patients (8%) in the NAC group and in 5 of the 50 patients (10%) in the ascorbic acid group and in 16 of the 50 patients (32%) in the placebo group ($\chi^2 = 12.292$, d.f. = 2, $P = 0.002$). Relative risk reduction against CIN in the NAC and ascorbic acid groups was 75% and 68.75%; the absolute risk reduction was 24% and 22%, respectively. The mean serum creatinine increased significantly in the placebo group (0.99 ± 0.21 to 1.15 ± 0.30 , $P = 0.001$) and non-significantly in the other groups (1.01 ± 0.20 to 1.15 ± 0.26 in the NAC group, 1.07 ± 0.31 to 1.12 ± 0.38 in the ascorbic acid group, $P = 0.9$).

Conclusions: Ascorbic acid monotherapy is equally effective as NAC in preventing CIN in patients undergoing coronary angioplasty.

Keywords: *N*-Acetyl cysteine; ascorbic acid; contrast induced nephropathy; Coronary angioplasty.

Introduction

Contrast-induced nephropathy (CIN) is the appearance or exacerbation of impairment in renal function occurring within days following intravascular administration of contrast media in the absence of alternative aetiology. Most studies have taken an increase in serum creatinine of more than 25% of baseline or an absolute increase of 0.5 mg/dl above

baseline as the required diagnostic criteria. It is the third most common cause of in-hospital acute renal failure after hypotension and surgery. Its incidence varies widely depending on the diagnostic criteria used, and the presence of associated risk factors: in normal renal function, the incidence is 1% with intravenous and 2–7% with intra-arterial administration of contrast media^[1–3]; it is higher (16%) in

non-azotemic diabetic patients^[4]; it may be as high as 33% in patients with pre-existing azotemia^[3]; and has been reported to occur in 3–16% of patients undergoing percutaneous coronary intervention (PCI)^[5,6].

Attempts to reverse CIN are usually unsuccessful and supportive care is the mainstay of therapy. A minority of patients become dialysis-dependent^[7]. CIN increases the costs of medical care, hospital stay, morbidity, and mortality^[8].

The optimal strategy to prevent CIN remains uncertain^[9]. At present, only hydration and use of iso-osmolar contrast agents have shown consistent benefit^[1]. Recently, considerable interest has resulted from the preliminary positive data on the effectiveness of prophylactic administration of NAC and fenoldopam^[10], with the former preventing direct oxidative tissue damage and the latter acting as a selective intra-renal vasodilator^[11]. NAC, however, failed to demonstrate a significant effect on the change of serum creatinine after cardiac catheterization. In patients with chronic renal insufficiency, along with intravenous fluids, it was found to be as effective as fluids alone in the prevention of CIN when moderate to high doses of contrast agent are used^[12].

The antioxidant ascorbic acid has been shown to attenuate renal damage caused by a variety of insults, such as post-ischaemic stress, in animals and has an extensive safety record as a dietary supplement in humans^[1]. Ascorbic acid is a potent, water-soluble antioxidant capable of scavenging a wide array of reactive oxygen species that can cause damage to macromolecules such as lipids, DNA, and proteins. In addition, ascorbic acid can regenerate other antioxidants, acting as a co-antioxidant^[1]. A recent study demonstrated that it prevents the complication of CIN after invasive coronary imaging procedures in patients with pre-existing renal dysfunction^[1].

This study was conducted to compare the effects of NAC and oral ascorbic acid monotherapy with placebo in reducing CIN incidence following coronary angioplasty.

Patients and methods

Consecutive patients undergoing clinically driven, non-emergent coronary angioplasty were eligible for inclusion. Patients were excluded for any of the following reasons: emergency angioplasty, pregnancy, and allergy to contrast agents.

The study was conducted in Faghihi hospital, affiliated to the Shiraz University of Medical Sciences. One hundred and fifty patients with any baseline serum creatinine were prospectively selected to receive oral NAC ($n=50$), oral ascorbic acid

($n=50$) or placebo ($n=50$). Patients were randomly (double-blind) assigned to receive either 600 mg p.o. NAC b.i.d.; 1.5 g p.o. ascorbic acid b.i.d. or placebo (as capsules containing starch) p.o. b.i.d. for 2 days starting on the day before the procedure (4 doses).

High fluid intake was recommended to all patients on the day before the procedure. Hydration with intravenous normal saline (50–125 ml/h) was started for all patients at least 4 h before and continued for 6 h after the procedure, the amount of which was adjusted according to the left ventricular ejection fraction (LVEF) and the presence of clinical heart failure in individual patients. The contrast agent was Omnipaque (Amersham Health, Cork, Ireland).

Baseline blood urea nitrogen (BUN) and creatinine were measured at the time of the procedure and at the follow-up test 96 h (4 days) after. All measurements were performed in a single hospital-based laboratory at Faghihi Hospital with the same methodology.

CIN was defined as a relative rise in serum creatinine at least 25% from the baseline. The secondary endpoint was an increase in serum creatinine following the coronary procedure with each of the prevention planes.

Data were reported as means (\pm SD) for continuous variables and as percentages for discrete variables. Continuous variables were analysed by ANOVA (analysis of covariants), Turkey test and chi-squared test. Logistic regression was performed with the primary end point of CIN as the independent variable. Statistical analyses were performed using SPSS 11.5 software program, and a P value of less than 0.05 was considered significant. This study was approved and monitored by the ethics committee of the Shiraz University of Medical Sciences.

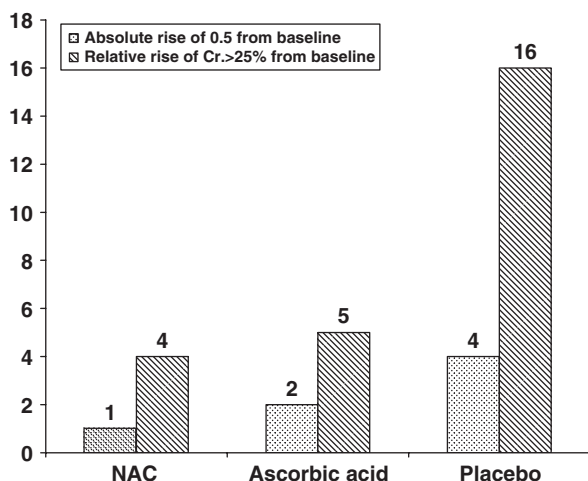
Results

Out of 150 patients, 104 patients were male (69.3%) and 46 (30.7%) were female. Their average baseline values are shown in Table 1. Increments of serum creatinine in the NAC, ascorbic acid, and placebo groups were 0.05 ± 0.21 , 0.05 ± 0.18 and 0.16 ± 0.17 ($P < 0.05$). A relative rise in serum creatinine of at least 25% from baseline was also significantly greater in the placebo group compared with the NAC or ascorbic acid groups ($\chi^2 = 12.292$, d.f. = 2, $P = 0.002$). The difference in the mean rise of serum creatinine between the test groups was negligible.

According to our criteria, CIN occurred in 25 patients (16.6%) in our sample. This incidence of CIN is considerably lower when a definition of at least a 0.5 mg/dl absolute increase is used, as illustrated in Fig. 1. Of these 25 patients, 4 (8%), 5 (10%) and 16 (32%) belonged to the NAC,

Table 1 Clinical, biochemical and procedural characteristics of the patients

Characteristic	NAC	Ascorbic acid	Placebo	P-value
Male/female ratio	2.84	1.63	2.57	ns
Mean age (years)	56.2 ± 6.6	56.8 ± 5.8	56.6 ± 5.7	ns
Diabetes mellitus (n,%)	7 (14)	6 (12)	5 (10)	ns
Mean contrast volume (ml)	333.1 ± 75	321.8 ± 64	311.8 ± 84	ns
Mean pre-angioplasty BUN (mg/dl)	15.7 ± 4	14.9 ± 4.6	15.2 ± 3.8	ns
Mean pre-angioplasty Cr (mg/dl)	1.01 ± 0.20	1.07 ± 0.31	0.99 ± 0.21	ns

**Figure 1** Incidence of contrast-induced nephropathy.

ascorbic acid and placebo groups, respectively ($P < 0.05$). Relative risk reduction against CIN in NAC and ascorbic acid was 75% and 68.75%, and the absolute risk reduction was 24% and 22%, respectively.

Among the 150 patients, 18 (12%) were diabetic, 2 of whom developed CIN ($P = 0.03$).

The patients who developed CIN had received a mean contrast amount of 367 ± 71 ml and those that did not develop CIN received 322 ± 66 ml ($P < 0.05$). It was also found that each 100 ml of contrast agent was associated with a 7.2% increased risk of CIN.

Of all the patients, 16 had pre-existing renal impairment (in non-diabetics $Cr \geq 1.5$ and in diabetics, $Cr \geq 1.3$) and 5 of these developed CIN (31.2%) ($P = 0.05$).

The study shows that pre-existing renal impairment, diabetes mellitus and contrast volume were the major risk factors predisposing to CIN.

Discussion and conclusion

This study shows that prophylactic oral administration of both ascorbic acid and NAC monotherapy lowers the incidence of CIN in patients undergoing coronary angioplasty. The incidence rate of CIN is subject to the definition used. A definition requiring 25% relative increase of baseline serum creatinine has

a CIN incidence following coronary intervention of 14.5% in unselected patients, and 37% in selected patients with a baseline serum creatinine of ≥ 1.8 mg/dl^[13,14], a definition of at least 0.5 mg/dl absolute increase in serum Cr lowers this incidence to 2.5% in patients with a baseline Cr of ≤ 1.9 mg/dl and 22.4% in patients with serum Cr of 2–2.9 mg/dl^[15]. Thus, the incidence of CIN is considerably lower when a definition of at least 0.5 mg/dl absolute increase is used. This difference was also noted in our study. This fact points to the need for a unified definition of CIN for better comparative analyses.

Contrary to other studies that measured serum Cr 2 days after the procedure, we opted to measure this at 96 h because serum Cr peaks at 3–5 days after exposure to contrast medium^[16,17]. The tendency for a higher occurrence of CIN among patients who had their serum creatinine concentration measured on days 3–5 compared with day 2 has also been supported elsewhere in the literature^[1]. No adjunctive medical or mechanical treatment has been proven to be efficacious in reducing the risk for CIN. The CIN Consensus Working Panel considered that, of the pharmacologic agents that have been evaluated, theophylline, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), ascorbic acid, and prostaglandin E₁ deserve further evaluation^[18].

Hydration is regarded as the only effective prophylactic strategy to reduce the incidence of radiocontrast nephropathy^[19], so this procedure is inevitably carried out before and after radiographic examination, particularly in high-risk patients. One study has shown that the incidence of radiocontrast nephropathy is significantly higher in patients assigned to free drinking than in those with hydration before contrast injection^[20].

Recent studies have demonstrated that isotonic (rather than half isotonic) hydration lowers CIN². All our patients received adequate water intake one day prior to the procedure and isotonic intravenous hydration for at least 4 h before and for 6 h after the procedure. An iso-osmolar, non-ionic agent (Omnipaque) rather than a low osmolar, non-ionic contrast medium was used because of its lower nephrotoxic effects.

Both animal and human studies implicate reactive oxygen species in the pathogenesis of

contrast-induced nephrotoxicity^[17]. Based on these studies, the effect of thiol-containing antioxidant NAC in preventing CIN was first tested by Tepel *et al.* in patients undergoing computed tomography^[21]. An impressive 90% reduction in incidence of CIN (≥ 0.5 mg/dl absolute serum Cr increase) was noted. Although several subsequent studies examining the effects of oral or intravenous NAC on the incidence of CIN in patients undergoing percutaneous coronary procedures showed disparate results, a meta-analysis of 7 randomized, placebo-controlled studies involving 805 patients showed that, compared to hydration alone, NAC significantly reduced the risk of CIN in patients with impaired renal function^[22,23].

Ascorbic acid has been shown to prevent CIN in this study. A recent randomized trial showed that the use of ascorbic acid was associated with a significant reduction (62%) in the rate of CIN among patients with renal insufficiency undergoing coronary angiography with or without intervention, but suggested further prospective studies to validate these preliminary results^[1].

Ascorbic acid is a water-soluble antioxidant capable of scavenging a wide array of reactive oxygen species that can cause damage to macromolecules such as lipids, DNA and proteins^[24]. In addition, ascorbic acid can regenerate other antioxidants^[25]. Its prophylactic use in patients undergoing catheterization would therefore provide a potentially cheaper, safe, and readily available medication, allowing wider patient coverage than the other antioxidants.

The dose used in this study (2 g p.o.) has a bioavailability of about 40% and the time of maximum excretion is 3 h^[25,26]. These doses of oral ascorbic acid have been shown to reverse endothelial vasomotor dysfunction 2 h after administration in patients with coronary artery disease and are, therefore, biologically relevant^[27].

The fact that we included only 150 patients is a limitation of our study. The low incidence of clinical CIN requiring supportive measures necessitated that we used a more liberal definition of CIN. Further studies should include larger samples, with a more stringent definition of CIN. We also used both NAC and ascorbic acid as monotherapy in this study. Further studies should be designed to evaluate the effects of combined pre-medication of ascorbic acid and NAC to note any additive effects.

From the results of this study, it can be concluded that ascorbic acid (a safe, well-tolerated, inexpensive, and readily available oral antioxidant), is equally effective as NAC in preventing post-coronary intervention CIN. The beneficial effects of ascorbic acid and NAC were observed to be higher than routine hydration even when a modern contrast medium with less nephrotoxicity was used. These findings may also

vindicate the hypothesis that CIN is caused, wholly or partly, by oxidative stress.

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