Prevention of Contrast-Induced Nephropathy with Ascorbic Acid

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Abstract

Background Some studies have shown that antioxidant ascorbic acid has renal protective effects, but the beneficial effects of contrast-induced nephropathy prevention remain to be clearly shown. Therefore, we aimed to determine whether ascorbic acid pretreatment reduces the risk of contrast-induced nephropathy in a high-risk population of patients with renal insufficiency undergoing coronary angiography.

Methods We conducted a prospective, randomized, controlled trial, involving 156 consecutive patients with chronic renal insufficiency (calculated estimated glomerular filtration rate <60 mL/min/1.73 m² and/or serum creatinine ≥ 1.1 mg/dL) undergoing coronary angiography. Patients were randomized to ascorbic acid (n=74, 3 g intravenous injection before the procedure and oral 1 g per day for 2 days after the procedure, ascorbic acid group) or sodium chloride alone (n=82, control group). All patients received pre-and postprocedure hydration.

Results There was no difference between the ascorbic acid group and control group in mean peak increase in serum creatinine measured within 48 hours after coronary angiography, the primary study end point (0.012 ± 0.146 vs 0.022 ± 0.212 mg/dL respectively, $p=0.216$). The incidence of contrast-induced nephropathy, a secondary end point defined as increase of either $\geq 25\%$ or ≥ 0.5 mg/dL in serum creatinine, was 5.4% in ascorbic acid-treated patients (4/74) and 6.3% in control group patients (6/82), a nonsignificant difference ($p=0.690$). There were also no differences between the 2 groups in the in-hospital clinical outcomes or length of hospital stay.

Conclusion Ascorbic acid pretreatment for short-term at high dose do not prevent renal function deterioration after administration of contrast medium in patients with baseline renal insufficiency undergoing coronary angiography.

Key words: contrast medium, nephropathy, angiography, ascorbic acid

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Introduction

Contrast-induced nephropathy (CIN) is a recognized complication after coronary angiography and intervention with iodinated contrast medium, which is the third leading cause of all hospital-acquired renal insufficiency, accounting for 10% (1) and is associated with prolonged hospitalization and adverse clinical outcomes (2).

We undertook a randomized, placebo-controlled trial of ascorbic acid for the prevention of CIN in a high-risk population of patients with renal insufficiency undergoing coronary

angiography.

Materials and Methods

Study population

The protocol of this study was approved by the Ethics Committee of Beijing Friendship Hospital, and written informed consent was obtained from all patients.

A total of 181 patients referred for coronary catheterization and/or coronary intervention were screened for eligibility from September 2008 through March 2009. Patients aged

≥ 18 years with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ (calculated using the MDRD formula) or baseline $\text{SCr} \geq 1.1 \text{ mg/dL}$ measured before coronary catheterization were considered to be eligible.

Patients were excluded for any of the following reasons: acute renal failure, end-stage renal disease requiring dialysis, unstable renal function, uncontrolled diabetes mellitus or hypertension, New York Heart Association class IV congestive heart failure or left ventricular ejection fraction (LVEF) $< 35\%$, intraarterial or intravenous administration of iodinated CM from 7 days before to 72 hours after the administration of the study agents, administration of any medication to prevent CIN such as NAC, or intake of nephrotoxic medications from 24 hours before to 24 hours after the administration of the study agent. Importantly, all patients who were recent ascorbic acid users (within 30 days before the procedure) were excluded.

Study protocol

All patients were hydrated with intravenous normal saline at a rate of 1 mg/kg per hour for 4 hours before and at least 12 hours after coronary catheterization. Patients randomized to ascorbic acid ($n=74$) received 3 g intravenous injection (IV) before the procedure, oral 0.5 g every 12 hours for 2 days after the procedure: once before coronary angiography, starting the morning before the procedure and twice after coronary angiography, beginning the evening of the day of the procedure. A total of 5 g of ascorbic acid was administered by IV and oral. Patients randomized to placebo ($n=82$) received normal saline alone. All patients were encouraged to drink if they were thirsty. The choice of the type of contrast medium (CM) was left to the interventional cardiologist performing the procedure, but use of a nonionic, low- or iso-osmolar contrast agent was encouraged.

Measurement of SCr

Serum creatinine was measured in the morning on the day before coronary angiography (day-1) and in the morning on days 1 and 2 after the procedure. Baseline SCr (day-1) was measured before initiating preprocedure hydration. The highest SCr value obtained between days 1 and 2 was used to calculate the change in SCr . Serum creatinine levels were performed using autoanalyzers located in the Department of Laboratory Medicine at Beijing Friendship Hospital.

Endpoints and definitions

The primary study end point was the mean peak increase in SCr within 48 hours after administration of contrast agent. The peak increase is the maximum difference of SCr between baseline and within 48 hours after contrast administration.

The secondary end point was the incidence of CIN, defined as a relative increase in baseline SCr of $\geq 25\%$ and/or an absolute increase of $\geq 0.5 \text{ mg/dL}$ ($\geq 44.2 \text{ }\mu\text{mol/L}$) within 48 hours after contrast administration. In addition, subgroup analyses were performed according to the presence of severe

renal impairment (defined as baseline $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), concomitant diabetes, the use of $\geq 150 \text{ mL}$ contrast media, reduced left ventricular systolic function (ejection fraction by echocardiography $\leq 50\%$), and advanced age (≥ 75 years), length of hospital stay and a composite clinical outcome of death, myocardial infarction, revascularization, dialysis, and occurrence of cerebral infarction.

Statistical analysis

Tests for significance were conducted using the t test for continuous variables and χ^2 test or Fisher exact test for categorical variables. All analyses were conducted using SPSS software version 11.5 (SPSS Inc, Chicago, IL).

Data are expressed as mean (SD). All tests are 2-tailed, with differences reported as significant if $p < 0.05$. The study analysis was a modified intention-to-treat and did not include protocol violators. Seven patients who did not return for follow-up laboratory tests were excluded.

Results

Patient population and baseline characteristics

Between September 2008 and March 2009, 181 patients with a basal $\text{CrCl} \leq 60 \text{ mL/min/1.73 m}^2$ and/or a $\text{SCr} \geq 1.1 \text{ mg/dL}$ were considered eligible for participation. Seven patients declined participation, and 18 were excluded because they had no laboratory test. Thus, 156 patients were randomized, 74 to receive ascorbic acid and 82 to receive normal saline alone (Fig. 1).

Baseline demographics and clinical characteristics were similar between the 2 groups, with no significant differences observed (Table 1).

Primary endpoint-peak increase in SCr

For patients receiving ascorbic acid, mean SCr increased from $1.264 \pm 0.418 \text{ mg/dL}$ at baseline to a maximum of $1.276 \pm 0.445 \text{ mg/dL}$ within 48 hours of the contrast procedure; this change was not significant ($p=0.862$). For patients receiving placebo, corresponding mean SCr levels were $1.258 \pm 0.364 \text{ mg/dL}$ and $1.280 \pm 0.512 \text{ mg/dL}$, respectively, with no difference between baseline and peak values ($p=0.434$) (Table 2). The maximum changes in SCr were not significantly different when the ascorbic acid and placebo groups were compared (0.012 ± 0.146 vs $0.022 \pm 0.212 \text{ mg/dL}$ respectively, $p=0.216$) (Table 2).

Secondary endpoint-incidence of CIN

The incidence of CIN after coronary intervention was found to be 6.4% in all patients (10/156); four patients in the control group (4/74, 5.4%) and six patients in the ascorbic acid group (6/82, 6.3%). There was no difference in CIN incidence between the 2 groups ($p=0.690$).

Figure 1. Flow chart of trial progress.

Adverse effects inhospital and length of hospital stay

Most of the adverse events in the study were nonserious and self-resolving with both groups. No serious cardiac adverse events (recatheterization, acute myocardial infarction, pulmonary edema, sudden death, etc.) were observed throughout the inhospital. There was also no difference between the 2 groups in the length of hospital stay after coronary catheterization (ascorbic acid, 4.5 ± 2.6 days, vs control, 5.1 ± 2.3 days; $p=0.380$).

Discussion

Most commonly, CIN is defined as an acute impairment of renal function manifested by an absolute increase in the serum creatinine (SCr) concentration of at least 0.5 mg/dL ($44.2 \mu\text{mol/L}$) or by a relative increase of at least 25% from the baseline value (3, 4). The incidence of CIN is low in the general population and has been calculated to be less than 2 percent (5). Patients at increased risk include those with renal impairment and diabetes, especially in combination. In such patients, the incidence is significantly higher, in the range of 12 to 50 percent (6, 7). Moderate to severe chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) $60 \text{ mL/min/1.73 m}^2$ [National Kidney Foundation, CKD stages 3 and 4 (8)] is the most important risk factor for the development of CIN. And CIN has been focused by radiologists, cardiologists, and nephrologists now.

Contrast-induced nephropathy results from direct renal tubular toxicity and renal medullary ischemia. Administration of contrast medium increases the production of nephrotoxic oxygen free radicals. Given the potential clinical severity of CIN, there has been considerable interest in the development of prophylaxis strategies to reduce the risk of contrast induced renal deterioration in at-risk populations, such as the

use of iso-osmolar contrast agents, hydration, vasodilators, antioxidants. Among these strategies, pharmacologic prophylactic strategies based on antioxidant properties have received considerable attention in recent years, with studies of N-acetylcysteine (NAC), for example, widely reported, albeit with conflicting findings (9, 10). Although the exact mechanism responsible for the nephroprotective action of NAC reported in some studies remains unclear, it has been suggested that protection is mediated via antioxidant and vasodilatory effects.

Ascorbic acid is a safe, well-tolerated, and readily available antioxidant, which has been shown to attenuate renal damage caused by a variety of insults, such as postischemic stress, cisplatin, aminoglycosides, and potassium bromate in animals (11-13). In addition to scavenging oxygen free radicals that mediate cell necrosis after myocardial infarction and after angioplasty, ascorbic acid may act as an antioxidant to inhibit ischemic cell death in the kidney. The results of a double-blind randomized-controlled trial (RCT) evaluating the use of the antioxidant ascorbic acid to prevent CIN in 231 patients undergoing coronary angiography are encouraging and deserve further study. The authors defined contrast-induced nephropathy by a 25% or higher rise in SCr level 2 to 5 days postprocedure and found that ascorbic acid significantly reduced the risk of this outcome (odds ratio, 0.38; 95% confidence interval, 0.17-0.85) (14). But the present study did not show the significant benefits of ascorbic acid in prophylaxis of CIN.

In this study, some mild CKD patients were enrolled and all patients received adequate hydration, so the incidence of CIN is lower than reported. Both the bioavailability and maintenance time of oral and intravenous ascorbic acid are not the same. Large doses of ascorbic acid short-range application may affect human body effective intake, influence ascorbic acid play antioxidant in renal function. Some limitations of the present study should be noted. It included only 156 patients from a single institution, which may be

Table 1. Baseline Patients Characteristics

Variable	Ascorbic acid group (n=74)	Control group (n= 82)	p
Age (y)	71.8±8.1	71.4±5.7	0.36
Sex (male/female)	51/23	47/35	0.11
BMI (kg/m ²)	26.48±3.22	27.29±3.85	0.59
SBP (mmHg)	130±20	132±22	0.79
HR (bpm)	67±10	68±11	0.95
LVEF (%)	49±12	48±14	0.63
SCr (mg/dL)	1.286±0.418	1.248±0.364	0.63
eGFR (ml/min/1.73m ²)	52.5±5.9	53.2±4.5	0.37
CM volume, mL	136.4±71.6	133.7±74.4	0.70
CM type n(%)			0.97
iodixanol	17(23.0)	19(23.2)	
Iopromide	32(43.2)	34(41.5)	
Iohexol	25(33.8)	29(35.4)	
PCI performed	51(68.9)	55(67.1)	0.31
Hydration given intra-venously, mL	700±200	680±300	0.52
Total amount of hydration, mL	1700±400	1600±600	0.26
Diabetes mellitus, n (%)	26(35.1)	28(34.1)	0.90
Hypertion, n (%)	54(73.0)	63(76.8)	0.58
Smoking, n (%)	41(55.4)	39(47.6)	0.33
ACEI or ARB, n (%)	60(81.1)	71(84.5)	0.35
Aspirin, n (%)	72(97.3)	80(97.6)	0.92
Statin, n (%)	52(70.3)	54(65.9)	0.52
Nitrate, n (%)	61(82.4)	70(85.4)	0.61
Diuretic, n (%)	8(10.8)	11(13.4)	0.62

BMI indicates body mass index; LVEF indicates left ventricular ejection fraction; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting-enzyme in-hibitor; and ARB, angiotensin receptor blocker. All other abbreviations are as defined in text.

Values are mean ± SD.

Table 2. Changes in Baseline SCr after Administration of Contrast Medium

SCr (mg/dL)	Ascorbic acid (n=74)	Control (n= 82)	p
Baseline	1.264±0.418	1.258±0.364	0.523
Follow-up	1.276±0.445	1.280±0.512	0.736
Absolute change	0.012±0.146	0.022±0.212	0.216

*SCr values in milligrams per deciliter are reported as mean (SD). 1mg/dL=88.4μmol/L.

the cause of the low incidence of CIN. And the trial is not double-blind. No further clinical follow-up was required after hospital discharge, most patients were discharged from the hospital at least 2 days after the procedure.

Conclusion

We concluded that short-term application of high-dose ascorbic acid do not prevent renal function deterioration after administration of contrast medium in patients with baseline renal insufficiency undergoing coronary angiography. Therefore, a large sample study may be needed to verify the benefits of ascorbic acid in CIN.

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

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