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Efficacy of allopurinol pretreatment for prevention of contrast-induced nephropathy: a randomized controlled trial

T. Erol [a,*], A. Tekin [a], M.T. Katırcıbaşı [a], N. Sezgin [b], M. Bilgi [a], G. Tekin [a], A. Zümrütdal [c], A.T. Sezgin [a], H. Müderrisoğlu [d]

[a] Baskent University Faculty of Medicine, Department of Cardiology, Adana, Turkey
[b] Baskent University Faculty of Medicine, Department of Biochemistry, Adana, Turkey
[c] Baskent University Faculty of Medicine, Department of Internal Medicine, Nephrology Division, Adana, Turkey
[d] Baskent University Faculty of Medicine, Department of Cardiology, Ankara, Turkey

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ABSTRACT

Background: Contrast-induced nephropathy (CIN) remains a common complication of radiographic procedures. Radiocontrast agents can cause a reduction in renal function that may be due to reactive oxygen species. Conflicting evidence suggests that administration of antioxidants prevents CIN.
Methods: We assessed the efficacy of allopurinol in preventing CIN. We prospectively randomized 159 patients with a serum creatinine concentration > 1.1 mg/dL undergoing cardiac catheterization/interventions to receive allopurinol (300 mg, p.o.) 24 h before administration of radiocontrast agent and hydration (1 mg/kg/h N/saline for 12 h pre- and post-contrast, n = 79), or hydration alone (1 mg/kg/h N/saline for 12 h pre- and post-contrast, n = 80).
Results: CIN occurred in 6 of 80 patients (7.5%) in the control group and no subjects in the allopurinol group ($p = 0.013$). In the allopurinol group, median serum creatinine concentration decreased significantly from 1.43 mg/dL [1.1–4.15 mg/dL] to 1.35 mg/dL [0.7–4.15 mg/dl] at 48 h and to 1.27 mg/dL [0.66–4.37 mg/dL] at 4 days after radiocontrast administration ($p < 0.0001$ and $p < 0.0001$ compared with baseline, respectively). In the control group, median serum creatinine concentration decreased non-significantly from 1.48 mg/dL [1.1–2.96 mg/dL] to 1.43 mg/dL [0.73–3.02 mg/dL] and to 1.45 mg/dL [0.86–3.71 mg/dL] ($p = 0.045$ and $p = 0.57$, respectively) 48 h and 4 days after radiocontrast administration.
Conclusions: Prophylactic oral administration of allopurinol, along with hydration, may protect against CIN in high-risk patients undergoing coronary procedures.

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1. Introduction

Contrast-induced nephropathy (CIN) is one of the most common causes of hospital-acquired acute renal failure, accounting for >10% of all cases and contributing to prolonged stay in hospital and increased medical costs [1,2]. This renal failure requires dialysis and carries a poor prognosis, including 40% in-hospital mortality and two-year survival of 19% [3–5].

Several interventions and drugs have been advocated to reduce contrast-associated morbidity and mortality, but very few have consistently shown benefit [6]. Periprocedural hydration and the use of a small amount of low-osmolality contrast agents have been considered to be the first-line treatment for CIN prevention.

Hypoxic injury to the renal medulla plays a major part in CIN development [7]. However, factors other than hypoxic medullary injury may be involved in CIN pathogenesis. They include tubular obstruction by radiocontrast media, precipitated crystals of oxalate or uric acid [8] and direct tubular toxicity (possibly involving the generation of oxygen free radicals and lipid peroxidation [8–10]). These processes may coexist and act in concert with hypoxic medullary injury [7].

Hyperuricemia has long been associated with renal disease [11]. In the literature, there is very little information about the relationship between hyperuricemia and CIN. Toprak et al. examined the effect of hyperuricemia on the prevalence of CIN in patients with chronic kidney disease undergoing elective coronary angiography [12]. They found that hyperuricemia increased the prevalence of CIN.

Allopurinol at standard doses is a competitive inhibitor of xanthine oxidase (XO), and is commonly used to treat gout and hyperuricemia [13]. It can block generation of oxygen radicals through inhibition of hypoxanthine catabolism. Because XO participates simultaneously in

Abbreviations: CIN, contrast-induced nephropathy; XO, xanthine oxidase; BUN, blood urea nitrogen.

* Corresponding author at: Başkent University, Faculty of Medicine, Department of Cardiology, Dadaloglu Mahallesi, 39. Sok. No. 6, 01250 Yuregir/Adana, Turkey. Tel.: +90 322 327 27 27; fax: +90 322 327 12 76.
E-mail address: tanselerol@yahoo.com (T. Erol).

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the production of uric acid and reactive oxygen species (ROS), inhibition of its activity by allopurinol has a beneficial effect on patients with endothelial dysfunction, heart failure and renal impairment [12]. Studies showing the beneficial effects of allopurinol in CIN are lacking.

In the present study, we sought to demonstrate the efficacy of prophylactic oral administration of allopurinol for CIN prevention in a prospective, randomized trial in patients with impairment of renal function undergoing invasive coronary procedures.

2. Material and Methods

2.1. Ethical approval of the study protocol

The Ethics Review Board of Baskent University approved the study protocol. Informed consent was obtained from all patients.

2.2. Patient population

We prospectively studied consecutive 159 patients with stable serum creatinine levels ≥1.1 mg/dL who underwent cardiac catheterization/intervention between October 2004 and August 2006. Exclusion criteria were patients: with acute myocardial infarction (AMI) requiring primary or rescue coronary intervention within 24 h; cardiogenic shock; acute renal failure; current peritoneal dialysis or hemodialysis; planned post-contrast dialysis; history of intravascular administration of contrast agents or anticipated re-administration of contrast agents within the following 4 days.

2.3. Study protocol

Patients were randomly assigned in a 1: 1 ratio to receive allopurinol (300 mg, p.o.) 24 h before administration of contrast agent and intravenous hydration (1 mg /kg/h N/saline for 12 h pre- and post-contrast), or intravenous hydration alone (1 mg /kg/h N/saline for 12 h pre- and post-contrast). Computer-generated random numbers determined randomization. The non-ionic, low-osmolarity, monomeric contrast medium iohexol (350 mg of iodine per milliliter; 780 mOsm per kilogram of water; Omnipauque, Amersham Health, Amersham, UK) was used in all cases. No patient received theophylline, dopamine, furosemide, acetylcysteine, or mannitol during the procedure. Serum creatinine, blood urea nitrogen (BUN), and uric acid were measured before administration of contrast agent and at 48 h and 96 h. Serum creatinine concentration immediately before coronary angiography was referred to as the "baseline level". CIN was defined as an increase in baseline serum creatinine concentration by 25% at 2 days or 4 days after radiocontrast administration.

2.4. Statistical analyses

Continuous variables with normal distribution are the mean value ± SD. The unpaired Student's *t*-test was done to determine differences between mean values for continuous variables if appropriate. Creatinine, BUN and uric acid concentrations were not normally distributed; therefore, the non-parametric Wilcoxon–Mann–Whitney *U*-test was used to assess differences between groups and the median values are given for these parameters. Categorical variables were analyzed by Fisher's exact test or chi-square test as appropriate. $p<0.05$ was considered significant. Data were analyzed with SPSS 9.0 for Windows (SPSS, Chicago, IL, USA).

3. Results

All patients enrolled were followed up as required by the study protocol. Ninety-six hours after angiography/intervention, 159 out of 168 patients had measurements of serum creatinine, BUN and uric acid were available for analyses.

There were no significant differences in baseline clinical characteristics between allopurinol and control groups (Table 1). The median serum creatinine concentration for all patients was 1.47 mg/dL (range, 1.10–4.15 mg/dL). In the control group, median serum creatinine concentration decreased non-significantly from 1.48 mg/dL [1.1–2.96 mg/dL] to 1.43 mg/dL [0.73–3.02 mg/dL] and to 1.45 mg/dL [0.86–3.71 mg/dL] ($p=0.045$ and $p=0.57$, respectively) 48 h and 4 days after radiocontrast administration. In the allopurinol group, median serum creatinine concentration decreased significantly from 1.43 mg/dL [1.1–4.15 mg/dL] to 1.35 mg/dL [0.7–4.15 mg/dl] at 48 h and to 1.27 mg/dL [0.66–4.37 mg/dL] at 4 days after radiocontrast administration ($p<0.0001$ and $p<0.0001$ compared with baseline, respectively)

Table 1
Baseline characteristics of the two treatment groups.

Characteristic	Allopurinol group (n = 79)	Control group (n = 80)	p
Age (years)	65 ± 9	65 ± 9	0.86
Male	18 (22.5%)	26 (32%)	0.88
Body mass index (kg/m^2)	27 ± 3.5	27 ± 4	0.93
Left ventricular ejection fraction (%)	51 ± 11	53 ± 9	0.27
Systemic hypertension	40 (50%)	47 (58%)	0.34
Diabetes mellitus	21 (25%)	22 (27%)	>0.9
Smoking	20 (25%)	21 (25%)	>0.9
Procedure			
Coronary angiography	70 (88%)	69 (86%)	0.84
Coronary angiography and *ad hoc* PCI	10 (12%)	12 (14%)	0.90
Volume of contrast media (mL)	121 ± 25	119 ± 26	0.64
Total amount of hydration (mL)	1874 ± 300	1804 ± 276	0.12
Drugs			
ACE inhibitor	33 (38%)	43 (47%)	0.15
Angiotensin-II receptor blocker	13 (17%)	13 (15%)	>0.9
Calcium-channel blocker	14 (21%)	10 (27%)	0.50
Beta-blocker	64 (76%)	63 (82%)	>0.9
Diuretic	10 (12%)	8 (10%)	0.83
Nitrate	41 (50%)	33 (41%)	0.26

PCI = percutenous coronary intervention; ACE = angiotensin-converting enzyme.

In the control group, the median BUN concentration decreased from 28 mg/dL [12–88 mg/dL] to 26 mg/dL [9–70 mg/dl] and to 27 mg/dL [10–80 mg/dl] at 48 h and 96 h after administration of the radiocontrast agent ($p<0.001$ and $p=0.108$ compared with baseline, respectively). In the allopurinol group, the median BUN concentration decreased from 25 mg/dL [10–76 mg/dL] to 22 mg/dL [7–69 mg/dL] and to 23 mg/dL [8–66 mg/dL], at 48 h and 96 h after administration of the radiocontrast agent ($p<0.0001$ and $p=0.093$ compared with baseline, respectively).

In the control group, the median uric acid concentration decreased from 6.8 mg/dL [3.5–13.5 mg/dL] to 6.3 mg/dL [3.1–10.4 mg/dL] and to 6.3 mg/dL [2.9–10.1 mg/dL], at 48 h and 96 h after administration of the radiocontrast agent ($p<0.0001$ and $p<0.0001$ compared with baseline, respectively). In the allopurinol group, mean uric acid concentration decreased from 6.8 mg/dL [3.3–17.2] to 5.48 mg/dL [2.1–14.6 mg/dL] and to 5.6 mg/dL [3–9.2 mg/dL], at 48 h and 96 h after administration of the radiocontrast agent ($p<0.0001$ and $p<0.0001$ compared with baseline, respectively).

In the control group, the mean creatinine clearance increased from 51.1 ± 17 mg/dL to 54.4 ± 23 mg/dL and to 53.4 ± 19 mg/dL, at 48 h and 96 h after administration of the radiocontrast agent ($p=0.002$ and $p=0.019$ compared with baseline, respectively). In the allopurinol group, mean creatinine clearance increased from 53.7 ± 14 mg/dL to 61.2 ± 23 mg/dL and to 61.7 ± 24 mg/dL, at 48 h and 96 h after administration of the radiocontrast agent ($p<0.0001$ and $p<0.0001$ compared with baseline, respectively). Creatinine clearance was significantly increased in the allopurinol group 96 h after administration of the radiocontrast agent ($p=0.004$) (Table 2).

CIN occurred in 6 of 80 patients (7.5%) in the control group (in 1 patient at 48 h and in 5 subjects between 48 h and 96 h) and in no patients in the allopurinol group ($p=0.013$) (Table 2). Baseline creatinine concentrations were not different between patients with CIN and patients without CIN (1.50 mg/dL [1.22–2.96] *vs* 1.46 mg/dL [1.1–4.15], $p=0.29$). Patients with CIN received a lower amount of contrast media compared with patients without CIN (97.5 ± 14.4 mL *vs* 121 ± 25 mL, $p=0.008$).

4. Discussion

The novel finding of the present study was that prophylactic oral administration of allopurinol reduced the prevalence of CIN in patients with impaired renal function. In addition, the absolute change

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