Allopurinol prophylactic therapy and the prevention of contrast-induced nephropathy in high-risk patients undergoing coronary angiography: A prospective randomized controlled trial

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Original Article

Abstract

BACKGROUND: Contrast-induced nephropathy (CIN) is considered to be a possibly severe complication of radiography and thus, remains to be the main cause of acute kidney injury (AKI) for inpatients. A clinical trial was executed to measure the preventive effect of allopurinol against CIN in high-risk patients undertaking coronary angiography.

METHODS: Through randomized controlled trial, 140 patients with at minimum two risk factors of CIN, undertaking coronary angiography, were randomly allocated to the allopurinol (n = 70) or control group (n = 70). Those in the allopurinol group received allopurinol (300 mg) a day before their coronary angiography and intravenous hydration for 12 hours before and after their procedure, while members of the control group only received intravenous hydration. Serum creatinine (SCr), blood urea nitrogen (BUN) and uric acid were measured before and 48 hours after the procedure. CIN was defined by a 25% increase in SCr or the concentration of > 0.5 mg/dl, 48 hours after coronary angiography.

RESULTS: CIN was observed in 8 (11.4%) patients in the allopurinol group and 11 (15.7%) patients in the control group. There was no significant difference in the incidence of CIN between the two groups at 48 hours after coronary angiography (P = 0.459). In the allopurinol group, the median SCr concentration decreased non-significantly from 1.16 mg/dl to 1.13 mg/dl, 48 hours after coronary angiography (P = 0.189). In the control group, the median SCr concentration increased significantly from 1.11 mg/dl to 1.2 mg/dl, 48 hours after coronary angiography (P < 0.001).

CONCLUSION: Allopurinol presents no considerable effectiveness over the hydration protocol for development of CIN in high-risk patients.

Keywords: Contrast Media, Allopurinol, Coronary Angiography

Introduction

Contrast-induced nephropathy (CIN) is a well-known common and severe complication of administering iodinated contrast after angiocardiography or radiology procedures.[1,2] CIN, in clinical studies, is defined as the 44.2 μmol/l (0.5 mg/dl) or 25% above baseline elevation of serum creatinine levels within 24 to 48 hours following iodinated contrast administration without an alternative cause.[3-5] The precise pathophysiological mechanisms of CIN are multifaceted and yet remain indistinct. The occurrence of CIN in patients who undergo coronary angiography is increasing, alternating from 2% up to 50% in the general population and high-risk patients, respectively, with situations such as chronic kidney disease (CKD) or certain risk factors.[2,3,6,7] The most serious risk factors of CIN comprise congestive heart failure (CHF), age > 75, diabetes mellitus (which is linked to enhanced risk, even in patients with preserved renal function), hypotension, hypertension, decreased renal perfusion, female gender, high-osmolar contrast, contrast volume, urgent versus planned

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percutaneous coronary intervention (PCI) and most importantly, CKD.[8,9] CIN is the third prominent cause of AKI for inpatients, featuring more than 10 % of all renal failure patients. It is also linked with enhanced risk of CKD progression and dialysis, increased morbidity and mortality and elevated healthcare costs.[3,10] Hence, preventive measures should be put in place for CIN, which yet poses a challenge among physicians. Currently, periprocedural intravenous hydration via iso-osmolar and/or low-osmolar contrast agents in place of high osmolar agents on the one hand, and limiting the dose of contrast media, on the other hand, are established approaches against CIN.[1,11] Several pharmacologic and therapeutic interventions have been practiced to lessen the incidence of CIN. Among them are N-acetyl-L-cysteine (NAC), calcium antagonists, nicorandil, ascorbic acid, diuretics, statins, sodium bicarbonate, fenoldopam, atrial natriuretic peptide, adenosine antagonists and other agents.[3,9,12-14] NAC among the mentioned solutions has gained substantial attention leading to several clinical trials and meta-analyses that attempted to evaluate the efficiency of NAC in preventing CIN. Nevertheless, NAC results have been controversial undermining the actual therapeutics suitable for this purpose.[1,3,15,16]

Allopurinol, as an inhibitor of xanthine oxidase (XO), has been widely used to treat gout and hyperuricemia. Recently, beneficial contributions of allopurinol into CIN prevention have been shown, so that it can protect kidney by inhibiting XO activity and blocking the generation of oxygen radicals and the production of uric acid.[10] Nevertheless, few reports are available about the preventive effect of allopurinol on CIN. Therefore, the aim of this study is to investigate whether allopurinol could reduce the incidence of CIN in high-risk patients undergoing coronary angiography.

Materials and Methods

The proposed protocol of this research was approved by the Ethics Committee of Qom University of Medical Sciences, Iran (Approval No: IRCT2014072318389N2), and a written informed consent was obtained from all patients prior to admission. This study was carried out in accordance with the principles of the Declaration of Helsinki.

This study was a prospective, open-label, randomized controlled trial. All patients (adults > 18 years) scheduled for coronary angiography (from October 2015 to March 2016) were screened against inclusion and exclusion criteria at Shahid Beheshti Hospital, Qom, Iran. Inclusion criteria encompassed at least moderate risk (risk score above 6) of CIN, as laid out by Mehran et al. risk score[7] which includes congestive heart failure, hypertension and diabetes mellitus (noted in their past medical history), age above 75 years and renal insufficiency which is defined as the estimated glomerular filtration rate (eGFR) less than 60 ml/minute/1.73m² or baseline serum creatinine more than 1.5 mg/dl. On the other hand, the exclusion criteria included end-stage renal insufficiency (eGFR less than 15 ml/minute), acute renal insufficiency, pregnancy and lactation, pulmonary oedema, cardiogenic shock, multiple myeloma, history of an allergic reaction to contrast agents or allopurinol, contrast media exposure within seven days before the procedure, uremia, renal failure resulting in receiving dialysis and the administration of NAC, metformin, dopamine, theophylline, sodium bicarbonate, mannitol, fenoldopam, diuretics and nephrotoxic medicines within 48 hours before a procedure. Prior to the procedure, a cardiologist on every participating patient conducted a comprehensive history and physical examination.

A total of 140 eligible patients were randomly assigned to either the allopurinol group or the control group, using a balanced block randomization protocol. Patients in the allopurinol group received 300 mg (100 mg, three times a day, oral, n = 70) allopurinol 24 hours before a procedure and intravenous hydration (1 ml/kg/hour) via normal saline, a maximum 100 ml/hour for 12 hours before and after coronary angiography, whereas patients in the control group (n = 70) received intravenous hydration via the same method. Serum creatinine (SCr), blood urea nitrogen (BUN) and uric acid were measured before coronary angiography and at 48 hours.

Several parameters were analyzed in the overall population. The glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault formula, (140–age) × weight (kg) / (SCr × 72), in men patients, and women patients adjusted by × 0.85. Kidney function was classified according to the stages set by the US National Kidney Foundation and defined by the eGFR value as normal kidney function: GFR ≥ 90 ml/minute and no proteinuria, mild kidney damage: GFR of 60–89 ml/minute with evidence of kidney damage, moderate damage: GFR of 30–59 ml/minute, severe damage: GFR of 15–29 ml/minute, and kidney failure (dialysis): GFR < 15 ml/minute/1.73m².

All tests were executed at the same laboratory using the same methodology. Coronary angiographies were accomplished through the femoral artery using the low osmolar nonionic contrast agent iohexol (Omnipaque, GE Healthcare, Cork, Ireland). Echocardiographic evaluations were also conducted for all patients before the procedure. Heart function was categorized according to the left ventricular ejection fraction as normal ≥ 55%, mild heart failure = 45%–54%, moderate heart failure = 30%–44%, and severe heart failure < 30%.[17]

The main endpoint of the study was the development of CIN, which is defined by elevated SCr levels at 44.2 μmol/l (0.5 mg/dl) or 25% above the baseline within 48 hours after coronary angiography without an alternative cause.[5] Secondary endpoints were determined to be changes of SCr, BUN, uric acid and eGFR within 48 hours after coronary angiography.

According to Erol et al.,[10] the sample size for the significance level of 0.050, with the power of 80%, has estimated approximately 70 patients in each group. Categorical data were presented as number and percentages, and the continuous data were stated in form of mean ± standard deviation (SD). Comparison of continuous variables was analyzed by a Student's t-test and Paired t-test for normally distributed, and the Mann-Whitney U-test and Wilcoxon rank sum test for non-normally distributed values. The Shapiro-Wilk test was used for testing the normality of distribution. The categorical variables were compared using the chi-square test or Fisher's exact test if the expected frequency was less than 5. The analysis of covariance (ANCOVA) was used to analyze mean differences between two groups after intervention with adjustment for baselines. Post-hoc pairwise comparisons were done with Sidak approach. Statistical significance was defined as P < 0.050. All calculations were analyzed with the SPSS for Windows (version 17, SPSS Inc., Chicago, IL, USA).

Results

Patient baseline characteristics are given in table 1. No significant differences were observed between the two groups for the baseline clinical characteristics.

In the allopurinol group, the median SCr concentration decreased non-significantly from 1.16 mg/dl to 1.13 mg/dl within 48 hours after angiography (P = 0.189). In the control group, the median SCr concentration increased significantly from 1.11 mg/dl to 1.2 mg/dl within 48 hours after angiography (P < 0.001) (Table 2).

Table 1. Baseline clinical and procedural characteristics of the patients

Variables	Allopurinol group (n = 70)	Control group (n = 70)	Total	P*
Men [n (%)]	54 (77.1)	46 (65.7)	100 (71.4)	0.134
Heart failure [n (%)]	62 (88.5)	63 (90.0)	125 (89.3)	0.425
Diabetes [n (%)]	29 (41.4)	27 (38.5)	56 (40.0)	0.730
Hypertension [n (%)]	45 (64.2)	42 (60.0)	87 (62.1)	0.601
Hypercholesterolemia [n (%)]	27 (38.5)	23 (32.8)	50 (35.7)	0.480
Smoking [n (%)]	23 (32.8)	16 (22.8)	39 (27.9)	0.187
Family history of heart disease [n (%)]	3 (4.2)	7 (10.0)	10 (7.1)	0.189
ACE inhibitor consumption[n (%)]	59 (84.2)	56 (80.0)	115 (82.1)	0.508
Statin consumption[n (%)]	55 (78.5)	56 (80.0)	111 (79.3)	0.835
Calcium blocker consumption[n (%)]	6 (8.5)	3 (4.2)	9 (6.4)	0.301
Iohexol [n (%)]	60 (85.7)	64 (91.4)	124 (88.6)	0.421
Age (year) (mean ± SD)	60.3 ± 12.6	62.1 ± 10.4	61.2 ± 11.6	0.356
Body mass index (kg/m^2) (mean ± SD)	26.8 ± 3.6	26.4 ± 3.2	26.6 ± 3.4	0.807
Hematocrit (mean ± SD)	43.6 ± 3.4	43.9 ± 4.7	43.7 ± 4.1	0.690
Mean arterial pressure (mmHg) (mean ± SD)	98.3 ± 12.8	96.3 ± 13.5	97.3 ± 13.2	0.353
Left ventricle function (%) (mean ± SD)	40.6 ± 9.7	41.8 ± 9.2	41.2 ± 9.4	0.425
Duration of suffering from hypertension (year) (mean ± SD)	3.1 ± 3.6	3.3 ± 3.8	3.2 ± 3.7	0.781
Duration of suffering from diabetes (year) (mean ± SD)	3.0 ± 4.5	2.7 ± 4.5	2.8 ± 4.5	0.648
Dose of contrast agent (ml) (mean ± SD)	41.1 ± 15.5	40.1 ± 14.4	41.1 ± 14.9	0.409

* Student's t-test for normally distributed and Mann-Whitney test for non-normally distributed values. The categorical variables were compared using chi-square test
ACE: Angiotensin-converting enzyme; SD: Standard deviation

Table 2. Biochemical and renal function changes before and 48 hours after coronary angiography

Variables	Allopurinol group (n = 70)	Control group (n = 70)	P[*]
SCr (mg/dl) (mean ± SD)			
Pre-angiography	1.2 ± 0.3	1.1 ± 0.3	0.161
48-hours post-angiography	1.1 ± 0.2	1.2 ± 0.2	0.043
P[**]	0.189	< 0.001	-
BUN (mg/dl) (mean ± SD)			
Pre-angiography	40.3 ± 17.2	38.8 ± 14.4	0.374
48-hours post-angiography	36.6 ± 15.1	41.6 ± 14.0	0.002
P[**]	0.023	0.096	-
Uric acid (mg/dl) (mean ± SD)			
Pre-angiography	6.1 ± 1.9	5.8 ± 1.5	0.874
48-hours post-angiography	5.1 ± 1.8	5.9 ± 1.7	0.010
P[**]	0.096	0.631	-
eGFR (ml/minute/1.73m^2) (mean ± SD)			
Pre-angiography	75.8 ± 28.1	74.2 ± 24.9	0.723
48-hours post-angiography	78.5 ± 25.4	70.5 ± 21.2	0.045
P[**]	0.129	0.045	-

[*] Student's t-test for normally distributed and Mann-Whitney test for non-normally distributed values; [**] Paired t-test for normally distributed and Wilcoxon rank sum test for non-normally distributed values.
SCr: Serum creatinine; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; SD: Standard deviation

In the allopurinol group, the median eGFR increased non-significantly from 75.8 ml/minute/1.73m² to 78.5 ml/minute/1.73m² within 48 hours after angiography (P = 0.129). In the control group, the median eGFR decreased significantly from 74.2 ml/minute/1.73m² to 70.5 ml/minute/1.73m² within 48 hours after angiography (P = 0.045) (Table 2). Overall, changes in SCr, eGFR, BUN, and uric acid within comparison groups before and after the study were compared in tables 2 and 3.

CIN occurred in 11 out of 70 (15.7%) patients in the control group and in 8 out of 70 (11.4%) patients in the allopurinol group. There was no significant difference in the incidence of CIN between the two groups within 48 hours after angiography (P = 0.459) (Figure 1).

Discussion

The hypothesis of this study is that allopurinol has a preventive effect on the development of CIN.

However, our results showed that prophylactic oral administration of allopurinol causes no significant reduction in CIN incidence as compared with the control group in high-risk populations for the development of CIN.
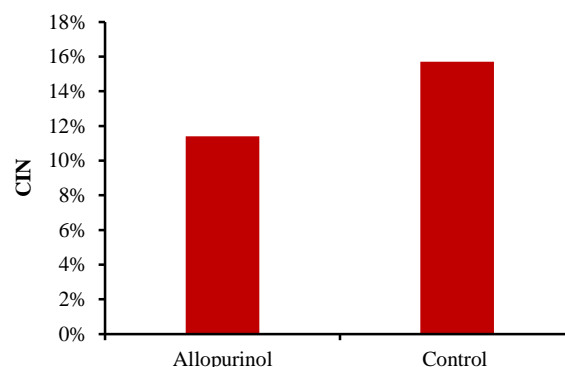

Figure 1. The incidence of contrast-induced nephropathy is not significant between treatment groups (P = 0.459)
CIN: Contrast-induced nephropathy

Table 3. Results of ANCOVA adjusting for age and baseline values of dependent variables

Group (Allopurinol vs. Control)	MMD	SE	95% CI for MMD	P[*]
SCr (mg/dl)	-0.106	0.026	(-0.157-0.055)	< 0.001
Uric acid (mg/dl)	-0.991	0.157	(-1.302-0.681)	< 0.001
BUN (mg/dl)	-5.786	2.042	(-9.824-1.748)	0.005
eGFR (ml/minute/1.73m^2)	6.785	2.050	(2.710-10.850)	0.001

[*] ANCOVA after adjusting for age and baseline values of dependent variables
MMD: Marginal mean differences (after intervention between two group); SE: Standard error of the mean; CI: Confidence interval; SCr: Serum creatinine; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate

Our study revealed significant differences in SCr, BUN, uric acid and eGFR within 48 hours after coronary angiography between two groups which may suggest the supportive effects of allopurinol on renal dysfunction. Our findings are inconsistent with the previous studies[10,18] reported that allopurinol along with hydration may prevent CIN in high-risk patients undergoing coronary procedures. In the study conducted by Erol et al., 79 patients with a serum creatinine concentration > 1.1 mg/dl received allopurinol (300 mg, oral) for 24 hours prior to cardiac catheterization and intravenous hydration (1 mg/kg/h normal saline for 12 hours pre- and post-contrast). In this study, the incidence of CIN within 48 h and 96 h after the procedure was significantly lower in allopurinol group compared to the control group.[10] Mean total dose of contrast agents used in the present study was about 40 ml, i.e. lower than those of previous studies.[10,18] These findings suggest that perhaps allopurinol is beneficial when administered at a different dosage or frequency in patients who received high doses of contrast agents. However, few studies have focused on preventive effects of allopurinol on CIN, so that more evidence on the efficacy of allopurinol in patients with high risk of CIN development are required.

It has been accepted that hydration and the use of low-osmolar contrast agents assist in preventing CIN in patients undergoing coronary angiography.[4,19] In this study, we also used these methods in treatment groups. The current contrast medium can be categorized by osmolality into high-osmolar contrast media (HOCM, ~ 1000-2500 mosmol/kg), low-osmolar contrast media (LOCM, ~ 400-800 mosmol/kg) and iso-osmolar (IOCM, 290 mosmol/kg). High osmolar contrast media was replaced by low/iso-osmolar contrast media due to better tolerability, fewer side effects and importantly to ensure a reduced incidence of CIN.[4,8] We also used Iohexol (low-osmolar, non-ionic contrast medium) to reduce complications and CIN incidence.

While the precise pathophysiology mechanism of CIN remains indistinct, possible direct and indirect pathophysiologic effects of contrast exposure that have been suggested include renal vasoconstriction, which initiates decreased oxygenation of the medulla causing ischemia and renal injury, direct tubular toxicity due to creation of oxygen free radicals that lead to acute tubular necrosis, and decreased in glomerular filtration because of alterations in tubule-glumeral regulatory mechanisms.[4,9,20,21] The exact mechanisms of the effect of allopurinol on CIN are unknown. However, it has been suggested that allopurinol protected the kidneys by attenuate through the production of oxygen free radicals caused by the xanthine inhibitory effects and also preserved the glomerular filtration rate through intra-renal regulatory mechanisms.[10]

Our study was constrained by a number of limitations. First, it was a single-centered non-blinded study. Second, in contrary to direct measurement, creatinine clearance was calculated using the Cockcroft-Gault formula. Third, the studied population was limited in size. Nevertheless, a larger multi-centered double-blinded randomized trial comprising other clinical settings would be beneficial in validating the beneficial effects of allopurinol in CIN prevention.

Conclusion

In conclusion, our findings revealed that allopurinol had no considerable effectiveness over hydration protocol in high-risk patients on CIN prevention. Nevertheless, according to the noteworthy variances observed in biochemical markers, we consider that the use of allopurinol could be effective on renal function and yet further controlled clinical trials are required to warrant regarding the comparative efficacy of allopurinol for the prevention of CIN.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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