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Research Article

Effects of Allopurinol in the Prevention of Periprocedural Myocardial Injury Following Elective Percutaneous Coronary Intervention: A Randomized Clinical Trial

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Abstract

Background: Periprocedural myocardial injury (PMI) after percutaneous coronary intervention (PCI) is a substantial health issue with a high mortality rate. Inflammation and oxidative stress are major contributing factors to PMI. Allopurinol inhibits xanthine oxidase (XO)-induced oxidative stress and has potential cardiovascular benefits.

Methods: This randomized clinical trial evaluated 110 patients admitted to elective PCI. Patients were assigned to receive either a 1200 mg loading dose of allopurinol 2 hours before the procedure (n = 55) or the standard pretreatment (n = 55). The creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) levels were measured in both groups at the baseline, 8, and 24 hours after PCI.

Results: There were no significant differences in the CK-MB levels at baseline (P = 0.71), 8 (P = 0.26), and 24 hours (P = 0.88) after PCI between the two groups. No significant changes in the cTnI levels at baseline (P = 0.26), 8 (P = 0.80), and 24 hours (P = 0.89) after the PCI were also noted. The mean difference for CK-MB and cTnI changes was not different between the two groups.

Conclusion: Our study revealed that allopurinol did not reduce cardiac-specific enzymes. Further studies are required to evaluate the impact of allopurinol on preventing PCI-related myocardial injury.

Introduction

Along with the progression of industrial societies and the growing burden of cardiovascular diseases, the rate of percutaneous coronary intervention (PCI) procedures is markedly increased. In this regard, PCI has a key role in occlusive coronary artery disease (CAD) management.[1,2] Despite improving PCI procedures, its adverse events remain at the center of attention. Among these, periprocedural myocardial injury (PMI) is the main complication that affects patients' early and late outcomes and leads to a higher mortality rate and morbidity.

As the 2018 ESC/ACCF/AHA/WHF statement on the Fourth Universal Definition of Myocardial Infarction, PMI was determined by the rise of cardiac enzymes more than the upper limit of the normal values after PCI. Based on this definition, the rate of PMI was reported to be about 15.8-30% in the studies. Several studies considered oxidative stress and inflammation as critical mechanisms involving PMI.[1,3,4]

Allopurinol attenuates oxidative stress by inhibiting xanthine oxidase (XO). Previously, allopurinol-related reduction in oxidative stress has been demonstrated to enhance myocardial contraction in patients with congestive heart failure (CHF).[5,6]

The anti-oxidant effects of allopurinol might result in improved endothelial and cardiac contractile function.[7] It has also been shown that allopurinol inhibits the progression of cardiomyopathy following ischemia in mice.[8] Allopurinol might exert anti-inflammatory effects by reducing interleukin 1-beta level, a contributing factor in cardiovascular disease.[9] These functions might decrease atherosclerosis progression and plaque instability, explaining the potential cardioprotective effects of allopurinol.[9,10]

According to the findings from a randomized clinical trial, allopurinol use leads to a reduction in a dose-dependent manner in myocardial infarction risk.[11] The anti-ischemia effects of allopurinol were also described in a randomized clinical trial on patients with chronic stable angina.[12]

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Despite the high percentage of PMI-related mortality and morbidity and increasing PCI procedures, there is no effective treatment for PMI prevention following PCI.

Concerning the mechanisms related to PMI and the potential cardioprotective effects of allopurinol, this study aimed to evaluate whether allopurinol could decrease cardiac biomarkers in patients undergoing elective PCI.

Methods

Ethics

The study was approved by the review board of Tabriz University of Medical Sciences and was registered in the clinical trials registry database with the identifier IRCT201412088307N11. All patients gave informed consent to enter the study. The trial was conducted in accordance Declaration of Helsinki and later revisions on ethics for clinical studies.[13]

Study design and setting

This single-blinded, randomized clinical trial was conducted in the Shahid Madani Heart Hospital, the main referral center for cardiovascular diseases in the northwest of Iran, for six months between October 2014 to March 2015.

Study population

Patients aged between 18 to 80 years with ischemic heart disease undergoing elective PCI, stent placement, and balloon angioplasty were included in the study.

The exclusion criteria included unsuccessful PCI, renal impairment (serum creatinine more than 2.5 mg/dl or patients on dialysis), hepatic dysfunction, serious infection, pregnancy, lactation, uncontrolled autoimmune and inflammatory disorders, cancer, cardiogenic shock, the elevation of creatine kinase-MB (CK-MB) or cardiac troponin I (cTnI) above the upper limit of the normal range prior to the PCI, history of coronary artery bypass grafting or acute myocardial infarction in the last three months, patients already on allopurinol, such as gout patients.

Study protocol and endpoints

Totally, 110 eligible patients were randomized to the allopurinol (n = 55) and control (n= 55) groups in a 1:1 ratio by block randomization (block size was 4) by an independent person who did not participate in the study. The main endpoint was comparing CK-MB and cTnI levels at baseline, 8, and 24 hours following PCI to evaluate the myocardial injury.

The usual pretreatment approaches for PCI, such as clopidogrel 300 mg, aspirin 325 mg, and intravenous unfractionated heparin (dosing based on weight) to achieve optimal activated coagulation time of 250–350 seconds, were used in the study groups. Moreover, both groups were administered 100 ± 20 ml radiocontrast agent iodixanol (visipaque™) in the course of PCI, and the usual practice for preventing contrast-induced nephropathy (CIN), such as 1200 mg N-acetyl cysteine twice a day with an infusion of normal saline or sodium bicarbonate before and after the procedure.

The intervention group received allopurinol 1200 mg orally two hours before the procedure. Interventional cardiologists performed PCIs based on the standard practice guidelines and were blinded to the allocation. Patients' baseline clinical and demographic characteristics such as age, sex, body mass index (BMI), family history of cardiovascular disease, drug and medical history, and laboratory data were documented in previously designed forms.

Blood sampling

The levels of CK-MB and cTnI were assessed at baseline (before allopurinol administration), 8, and 24 hours after PCI to detect the myocardial injury during PCI according to the AHA/ACCF guidelines.[1] The lower detection limits of blood levels were 1 U/L for CK-MB and 0.1 ng/ml for cTnI.

Study power and sample size

We determined the study power by G-Power (version 3.1.9.2), considering a type I error rate $\alpha = 0.05$, $n = 108$, two groups, and three consecutive sampling periods. The power ($1-\beta$ error) for the CK-MB test was 99% with a partial eta-squared ($\eta 2$) of 0.1 and an estimated effect size (F) of 0.3. Also, for troponin-I (cTnI) with partial $\eta 2$ of 0.5 and estimated effect size (F) of 1, the power was 100%.

Statistical analysis

SPSS 16.0 (Chicago, SPSS Inc., 2007) was used for data analysis. Initially, the Kolmogorov–Smirnov test was conducted to determine the normal distribution of data. Repeated measures analysis of variance (ANOVA) was conducted with Bonferroni correction for multiple comparisons to test the effects of time and groups. The means between the groups were compared with Mann–Whitney or independent sample t-tests. Fisher's exact and Chi-square tests were used for groups of categorical data. Continuous data were reported as mean ± standard deviation (SD). The P-values below 0.05 were considered to be statistically significant.

Results

Within the study period, 119 patients were screened. Of them, 9 patients did not undergo randomization due to pre-PCI rise of cardiac biomarkers (n = 5), renal impairment (n = 3), and serious infection (n = 1). Accordingly, 110 patients were randomly assigned to the intervention group (n = 55) or the control group (n = 55). In the intervention group, two patients were excluded due to unsuccessful PCI. Finally, analysis was performed on 108 patients (Figure 1).

The mean ± SDs of the age of patients was 63 ± 10.8 years in the allopurinol and 61.6 ± 9.7 in the control groups (P = 0.49). The majority of the patients were male, with 60.3 % and 63.6% in the intervention and

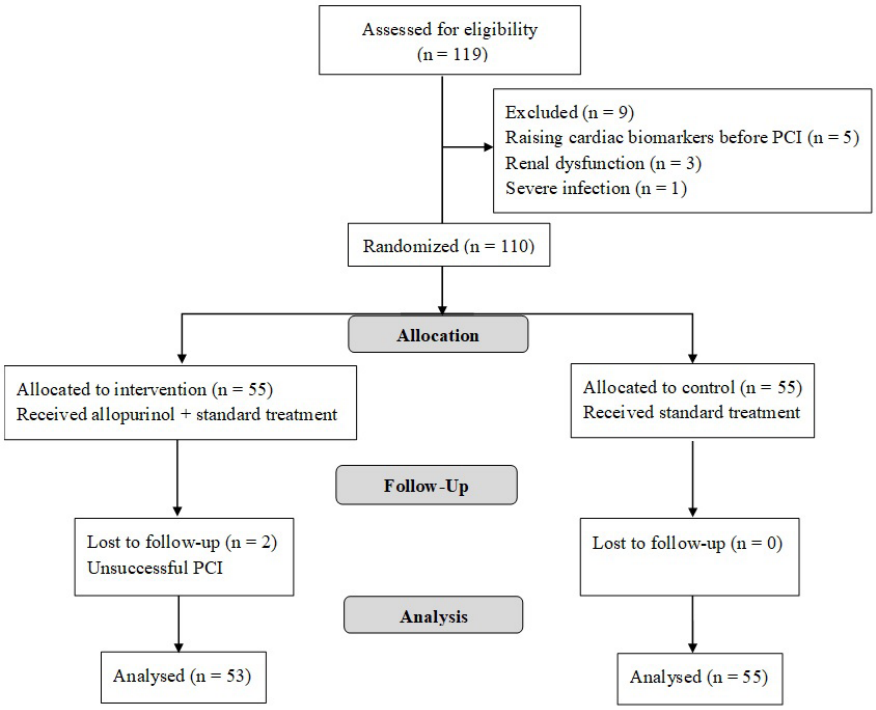

Figure 1. CONSORT flow diagram. PCI, percutaneous coronary intervention.

control groups, respectively (P = 0.66). Comparing the baseline demographic and clinical characteristics showed similarities between the two groups (Table 1).

The majority of patients have only one vessel that underwent angioplasty (85.3% in the intervention group and 81.9% in the control group). The main vessels that underwent angioplasty were left anterior descending (LAD) [48.4% in the intervention vs. 41% in the control group, P = 0.19] and right coronary artery (RCA) [26.8% in the intervention vs. 22.7% in the control group, P = 0.58]. Left circumflex (LCX) was stented in 9.7% and 18.2% of patients in the intervention and control groups, respectively (P = 0.73). Other stented vessels include LAD plus RCA, LAD plus LCX, and RCA plus LCX (14.7% vs. 18.2% in the intervention and control groups, respectively, P = 0.24).

Based on the 2018 ESC/ACCF/AHA/WHF definition, PMI described as the post-PCI cTn rise of ≥5 × 99th percentile upper reference limit, was seen in 3.6% (n = 2) in the control group and 5.6% (n = 3) in the intervention group, which was not statistically significant (P = 0.678). The rise in CK-MB levels was detected in 10.9% (n = 6) and 22.6% (n = 12) of patients in the intervention and control groups, respectively (P = 0.102).

The baseline level of CK-MB was similar in both intervention and control groups (P = 0.71). After PCI, CK-MB levels at 8 (P = 0.26) and 24 hours (P = 0.88) did not significantly differ in the study groups. Furthermore, the mean difference for CK-MB changes at baseline and 8 hours (P = 0.21), baseline and 24 hours (P = 0.75), and 8 and 24 hours (P = 0.14) following the procedure was not significant between the two groups (Table 2).

The baseline level of cTnI was similar in both groups (P = 0.26). Also, no significant difference was observed in levels of cTnI at 8 (P = 0.80) and 24 hours (P = 0.89) after PCI between the two study groups. The changes in cTnI mean

Table 1. Baseline demographic and clinical data of patients.

Demographic/Clinical Data	Intervention (n = 53)	Control (n = 55)	P-value
Age (y), mean ± SD	63 ± 10.8	61.6 ± 9.7	0.49
Sex, male, n (%)	32 (60.3)	35 (63.6)	0.66
BMI (kg/m2), mean ± SD	27.3 ± 3.4	28.0 ± 3.5	0.37
Serum creatinine (mg/dL), mean ± SD	1.05 ± .24	1.0 ± 0.18	0.18
BUN (mg/dL), mean ± SD	15.9 ± 3.5	16.7 ± 5.8	0.47
Hematocrit (%), mean ± SD	13.6 ± 1.6	14.0 ± 1.7	0.26
FBS (mg/dL), mean ± SD	140.3 ± 26.3	137.2 ± 76.8	0.83
Hypertension, n (%)	30 (56.0)	35 (63.6)	0.45
Family history for CVD, n (%)	6 (11.3)	7 (12.7)	0.76
Diabetes mellitus, n (%)	10 (18.8)	17 (30.9)	0.14
Ejection fraction (%), mean ± SD	48.7 ± 5.5	47.5 ±8.0	0.35

BMI, body mass index; BUN, blood urea nitrogen; CVD; cardiovascular disease; FBS, fasting blood sugar; SD, standard deviation.

Table 2. Mean CK-MB levels at baseline, 8, and 24 hours after PCI in the study groups.

CK-MB level (mean ± SD)	Intervention	Control	P-value
Baseline	20.9 ± 6.4	21.3 ± 5.0	0.71
At 8 hours	25.6 ± 11.4	23.3 ± 9.5	0.26
At 24 hours	25.1 ± 13.5	24.8 ± 10.8	0.88
Mean difference of baseline and 8 hours	4.7 ± 11.7	2.0 ± 10.4	0.21
Mean difference of baseline and 24 hours	4.2 ± 12.8	3.5 ± 11.7	0.75
Mean difference of 8 and 24 hours	4.2 ± 12.8	1.4 ± 4.5	0.14

CK-MB, creatine kinase-MB; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 3. Mean cTnI levels at baseline, 8, and 24 hours after PCI in the study groups.

cTnI nlevel (mean ± SD)	Intervention	Control	P-value
Baseline	0.1 ± 0.5	0.2 ± 0.4	0.26
At 8 hours	0.2 ± 0.4	0.2 ± 0.5	0.8
At 24 hours	0.3 ± 0.7	0.4 ± 1.2	0.89
Mean difference of baseline to 8 hours	0.13 ± 0.4	0.03 ± 0.2	0.19
Mean difference of baseline to 24 hours	0.2 ± 0.7	0.2 ± 0.8	0.78
Mean difference of 8 to 24 hours	0.1 ± 0.3	0.14 ± 0.8	0.68

cTnI, cardiac troponin I; PCI, percutaneous coronary intervention; SD, standard deviation.

difference at baseline and 8 hours (P=0.19), baseline and 24 hours (P = 0.78), and 8 and 24 hours (P = 0.68) were not significant between the study groups (Table 3).

With respect to adverse drug reactions, no significant difference was observed between the two groups (P > 0.05). No major adverse cardiac event, such as death, hospitalization due to cardiovascular reasons, or stroke, occurred in both groups during the 28-day follow-up period.

Discussion

To the best of our knowledge, this randomized controlled trial was the first study investigating the effects of allopurinol in preventing PCI-related PMI. This study could not support the use of allopurinol to prevent PCI-related PMI.

Large studies have described the clinical importance of elevated cardiac biomarkers after PCI.[14,15] The meta-analysis on 23,230 patients in 11 randomized clinical trials revealed that >5 times increase in CK-MB levels after elective PCI resulted in 3.1 folds death rate increase.[14] A meta-analysis on 15,581 patients from 20 randomized clinical trials revealed that cardiac troponins rise significantly associated with the mortality rate after PCI (odds ratio [OR], 1.35; 4.4 vs. 3.3%, P = 0.001).[15]

Hyperuricemia is associated with pro-inflammatory states and endothelial dysfunction. A meta-analysis of 9 trials on 334 patients indicated that allopurinol significantly improved endothelial-dependent vasodilation.[16] Probable mechanisms for cardiovascular benefits of allopurinol are reducing serum uric acid concentration, inhibiting atherosclerotic plaque rupture and endothelial dysfunction by attenuating XO-mediated synthesis of reactive oxygen species, and increasing local tissue accessibility of adenosine triphosphate and oxygen by blocking purine catabolism.[7,10,17,18]

In a double-blind, randomized, placebo-controlled trial on 66 patients with ischemic heart disease and left ventricular hypertrophy (LVH), the effects of 600 mg daily allopurinol were compared with place for 9 months. Data analysis showed that allopurinol reverts LVH, reduces left ventricular end-systolic volume, and improves endothelial function, which might reduce future cardiovascular events and mortality.[19] Another large retrospective cohort study on 25090 patients with gout and heart failure history showed that allopurinol reduces heart failure readmissions or death rates for any reason.[6] In a multicenter randomized controlled trial, febuxostat and allopurinol decreased heart failure-related death and re-hospitalization in 272 patients with serum uric acid >7.0 mg/dl (83.7% vs. 85.8%, P = 0.386).[20] Conversely, in a randomized, double-blind, placebo-controlled trial by Lea Borgi *et al.*[21], allopurinol (300–600 mg/day) did not affect endothelial function in patients with serum uric acid ≥5.0 mg/dL and BMI ≥25 kg/m2 revealed. Unlike our study, patients with cardiovascular diseases did not enter this study.

Coronary vascular endothelial dysfunction is commonly observed in patients who have CAD. A study in patients with stable CAD indicated that oxypurinol improves coronary vascular endothelial dysfunction.[22] Previous studies supported the anti-ischemic effects of long-term allopurinol administration.[12,23,24] A randomized controlled clinical trial study in 65 patients with a positive exercise tolerance test, angiography-confirmed CAD, and chronic stable angina indicated that 600 mg daily allopurinol for 6 weeks increased the time to angina, ST depression, and total exercise time.[12] Rajendra *et al.*[22] studied potential anti-ischemic mechanisms of allopurinol in 80 patients with stable angina. Data analysis showed that 600 mg daily allopurinol for 8 weeks improves endothelial-dependent vasodilation.

Furthermore, Huang *et al.*[24] carried out a randomized controlled trial on 100 patients to evaluate allopurinol efficacy in patients with the acute coronary syndrome. In the intervention group, patients received allopurinol 600 mg/day for 14 days, followed by 200 mg/day to completion

of a 4-week course in addition to the standard treatment in the control group. It has been indicated that allopurinol could improve oxidative stress and inflammatory reactions. During two years, the rate of cardiovascular events was 10% and 30% in the intervention and control groups, respectively.

The beneficial effects of allopurinol in myocardial reperfusion therapy have been observed in several animal studies.[25,26] Furthermore, in a study on 38 patients with acute myocardial infarction, administration of 400 mg oral allopurinol 60 min before percutaneous transluminal coronary angioplasty inhibited free radical production during the reperfusion therapy.[27]

In another study on 40 patients with ST-elevation myocardial infarction, allopurinol with 400 mg loading and 100 mg maintenance doses decreased troponin I and CK-MB levels after one month. Furthermore, it has significant beneficial effects on reducing major adverse cardiac events.[28] A placebo-controlled randomized clinical trial was carried out on 254 patients with CAD to study the impact of allopurinol pre-administration on cardiac biomarkers in patients undergoing elective PCI. Patients received allopurinol 600 mg orally before PCI and on PCI day. The levels of CK-MB and cTnI were assessed the day before PCI, 8, and 16 hours after the intervention. In line with our results, they showed that allopurinol usage is not linked with reduced cardiac biomarkers.[29] Of note, the doses of allopurinol were higher in our study (1200 mg).

In a recent randomized clinical trial on 100 patients with non-ST elevation myocardial infarction, allopurinol at a dose of 600 mg orally on the first day, followed by 300 mg daily for two days, did not significantly reduce cTnI levels. In this study, patients did not undergo PCI, and the aim differed from the current study, in which the role of allopurinol was evaluated in reducing PMI.[30]

Our study might suffer from some limitations. First, because of the cost and time limitations, the duration and the sample size of the study were limited. Second, this study did not evaluate inflammatory biomarkers such as hs-CRP levels. Third, given the limited accessibility, our study was not placebo-controlled.

Conclusion

Our study showed that allopurinol administration in patients undergoing elective PCI has no effects on cardiac-specific enzymes, including CK-MB and cTnI. Further well-designed clinical trials with a larger sample size are required to assess the role of allopurinol in post-PCI myocardial injury.

Ethical Issues

This study was approved by the ethics committee of Tabriz University of Medical Sciences and was registered in the clinical trials registry database with the identifier IRCT201412088307N11. All methods in this study were performed in accordance with the declaration of Helsinki. Participants signed an informed consent form before recruitment.

Data Sharing

The data of this study can be accessed on request from the corresponding author.

Author Contributions

Naser Aslanabadi: Conceptualization, Resources, Supervision. Elnaz Khani: Writing - Original Draft. Sajad Khiali: Writing - Original Draft. Haleh Rezaee: Formal Analysis, Writing - Review & Editing. Saba Pishdad: Investigation. Taher Entezari-Maleki: Supervision, Writing - Review & Editing.

Conflict of Interest

The authors report no conflicts of interest.

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