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Impact of Allopurinol Pretreatment on Coronary Blood Flow and Revascularization Outcomes after Percutaneous Coronary Intervention in Acute STEMI Patients: A Randomized Double Blind Clinical Trial

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Original Article

Abstract

INTRODUCTION: The generation of reactive oxygen species, which is induced by the activation of the xanthine oxidase (XO) enzymatic system, is one of the primary causes of ischemia-reperfusion injury for an ischemic heart. Allopurinol, as an XO inhibitor, plays an inhibitory role in free radical production in ST-elevation myocardial infarction (STEMI) patients. The aim of this study is to evaluate the impact of allopurinol pre-treatment on post-revascularization outcomes in patients admitted with STEMI

METHOD: Ninety patients with acute STEMI were enrolled in this randomized double-blind clinical trial and divided into two equal groups. The allopurinol group received a 600 mg allopurinol loading dose before the emergency PCI, and the control group received a placebo medication of the same shape. Thrombolysis in Myocardial Infarction (TIMI) flow, ECG changes, troponin level, and the occurrence of major cardiac events (MACE) during a 1-month follow-up were assessed.

RESULTS: In the end, 81 patients were analyzed. The mean age of the patients was 59.52(11.31) and 61.3(9.25) in the allopurinol and control groups, respectively ($p = 0.49$). The troponin level 48 hours after the PCI and ST-elevation regression showed no significant difference between the groups [($p = 0.25$) and ($p = 0.21$), respectively]. TIMI flow had improved in the allopurinol group compared to the placebo ($p = 0.02$). The PCI success rate was 78.6% and 61.5% in the case and control groups, respectively ($p = 0.09$). MACE and other clinical outcomes were similar between the groups ($p > 0.05$).

CONCLUSION: This study revealed that allopurinol pre-treatment could improve TIMI flow in patients undergoing primary or rescue PCI in an acute STEMI setting.

Keywords: Allopurinol, Percutaneous coronary intervention, STEMI, TIMI flow

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Introduction

Today, ischemic heart disease (IHD) is considered a public health problem and the main cause of morbidity and mortality worldwide [1, 2]. In this regard, acute ST-segment elevation myocardial infarction (STEMI) is the most common and important component of coronary artery diseases (CAD) [3]. Reperfusion therapy with percutaneous coronary intervention (PCI) is the best treatment for STEMI patients [4]; although establishing

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coronary blood flow can also induce a secondary injury known as myocardial ischemia-reperfusion injury (IRI) [5]. In fact, IRI is one of the main causes of decreased clinical benefit and mortality in patients with acute STEMI despite appropriate reperfusion therapy [4]. The generation of reactive oxygen species (ROS) by the activation of the xanthine oxidase (XO) enzymatic system is one of the major causes of IRI in the ischemic myocardium [6]. In the list of anti-inflammatory medications, allopurinol, as an XO inhibitor, has a questionable role in the treatment of cardiovascular diseases [7]. Concerning the effect of allopurinol on cardiac biomarkers and free radical production in STEMI patients who underwent primary PCI, the results were in favor of its beneficial effects [8,9]; however, this was not confirmed in patients who were candidates for elective PCI [10].

To the authors' knowledge, this is one of the first studies to investigate the pre-treatment effect of allopurinol on coronary reperfusion in STEMI patients undergoing PCI based on Thrombolysis in Myocardial Infarction (TIMI) flow grading. Thus, in this study, the authors aimed to assess the impact of allopurinol pre-treatment on revascularization outcomes, according to TI.

Materials and Methods

Study type and ethics

This study, as a randomized double-blind clinical trial, was reviewed and approved by the research ethics committees at the School of Medicine - Isfahan University of Medical Sciences, Isfahan, Iran (approval ID: IR.MUI.MED.REC.1398.138), and registered in the Iranian Registry of Clinical Trials (http://www.irct.ir) with the IRCT number: IRCT20181228042155N1.

Study Population

The study was conducted at the Shahid Chamran Heart Center, Isfahan, Iran, the largest referral hospital in central Iran, from August 2019 to May 2020. Patients aged between 18 to 85 years with an acute STEMI diagnosis who were planned for emergency PCI as primary and rescue therapy were included in the study.

A diagnosis of STEMI was defined by typical chest pain relating to ischemia with an onset time of less than 24 hours and at least 1 mm ST-segment elevation in two or more contiguous leads simultaneously, accompanied by elevated cardiac biomarkers [11]. Exclusion criteria included presenting to the hospital more than 24 hours after symptom onset, a history of coronary artery bypass graft (CABG), cardiogenic shock, renal dysfunction (glomerular filtration rate of 60 mL/min or less or serum creatinine above 2 mg/dl), inflammatory or autoimmune diseases, severe infection, hepatic dysfunction, a history of gout or allopurinol use, and taking warfarin, azathioprine, or 6-mercaptopurine.

Study design

A total of 90 patients were randomized into two equal groups using a random number table method in the emergency unit. In Group I (n = 45), 600 mg of allopurinol (Hakim Pharmaceutical Co., Tehran, Iran) was administered orally immediately after admission and before transfer to the catheterization laboratory. Patients in Group II or the control group (n = 45) were treated with a placebo (made by Isfahan Pharmacy faculty, Isfahan University of Medical Sciences, Isfahan, Iran) which was matched with allopurinol tablets in all characteristics. Both groups received the standard pre-treatment protocol for PCI in an acute STEMI setting including 325 mg of acetylsalicylic acid, a 600 mg loading dose of Clopidogrel, and 80 mg of Atorvastatin. PCI was performed with or without balloon angioplasty and drug-eluting stents (DES) with the aim of achieving angiographic success defined as residual stenosis less than 20% in the presence of grade 3 TIMI flow without major intimal dissection. As a confounding factor, procedures requiring glycoprotein (GP) IIb/IIIa inhibitors injections were excluded from the study. In Group I, allopurinol 100 mg

daily and in Group II the matched placebo was continued for one month in addition to the administration of aspirin (81 mg), clopidogrel (75 mg to 150 mg), statins, beta-blockers, and angiotensin-converting enzyme (ACE)-inhibitors or angiotensin II receptor blocker (Figure 1). The same blinded interventional cardiologists conducted all PCIs in both groups.

Endpoints

The primary endpoints were revascularization outcomes based on TIMI flow grade and ST-segment elevation recovery. TIMI flow grade 0 is defined as no perfusion, grade 1 as penetration without perfusion, grade 2 as partial perfusion, and grade 3 as complete perfusion [12]. A 12-lead standard ECG was obtained at admission time and 30 minutes after PCI, and ST-segment elevation recovery was calculated 20 milliseconds after the end of the QRS complex. All angiographic views and ECGs were assessed by a blinded interventionist. The secondary endpoints were the incidence of major adverse cardiac events (MACEs) including death, MI, and ischemic stroke for one month follow-up as well as the level of troponin 48 hours after revascularization. Follow-up data would be obtained from periodic visits and telephone interviews.

Baseline characteristics data, including sex, age, past medical history, level of MI, time from the onset of symptoms to the performance of PCI, number of leads with ST-segment elevation, admission left ventricular ejection fraction (LVEF), and laboratory data were recorded. Angiographic and procedural information such as target vessel, CAD severity, lesion length and diameter, type of lesion (according to AHA classification), and type of intervention, as well as mechanical and electrical complications, were also investigated.

Statistical Analysis

The obtained data were collected in a checklist and entered into SPSS software (version 22, IBM Corporation, Armonk, NY, USA) for analysis. The numeric variables were showed as mean [standard deviation (SD)]. Kolmogorov–Smirnov test was used to evaluate the normal distribution. Differences in numerical variables between the case and control groups were analyzed using the independent-sample t-test for normally distributed variables. If the distribution was not normal, the Mann-Whitney test was used. Nominal and ordinal variables were presented as absolute numbers (percentages). Nominal and ordinal variables were analyzed between groups using the chi-square, Cochran-Armitage test, and Mann-Whitney test, respectively. A p-value of less than 0.05 was considered as the level of significance. All of the statistical analyses were performed by an analyzer who was blind to the details of the research.

Results

Figure 1 shows the study consort diagram, and Table 1 shows the general characteristics of the participants. In total, 81 patients with acute STEMI completed the study. The mean age of the study population was 59.52 (11.31) and 61.3 (9.25) in the case and control groups, respectively ($p = 0.49$). Most participants in both groups were male (more than 80 percent). There was no statistically significant difference between the two groups in general characteristics such as age, gender, cardio metabolic past history, smoking status, hemoglobin level, creatinine level, and platelet count. Regarding infarct levels, ST elevation involved lead counts, pre-PCI LVEF, pre-PCI arrhythmia occurrence, and PCI indication setting (primary and rescue), there were no significant differences between the groups (Table 2). Table 3 shows angiographic and PCI characteristics of patients, including coronary artery severity, vessels that underwent PCI, lesion type, pre-PCI TIMI flow, and culprit vessels diameter and length, as well as stent types, diameters, and lengths. There was also no notable difference between these parameters in the groups.

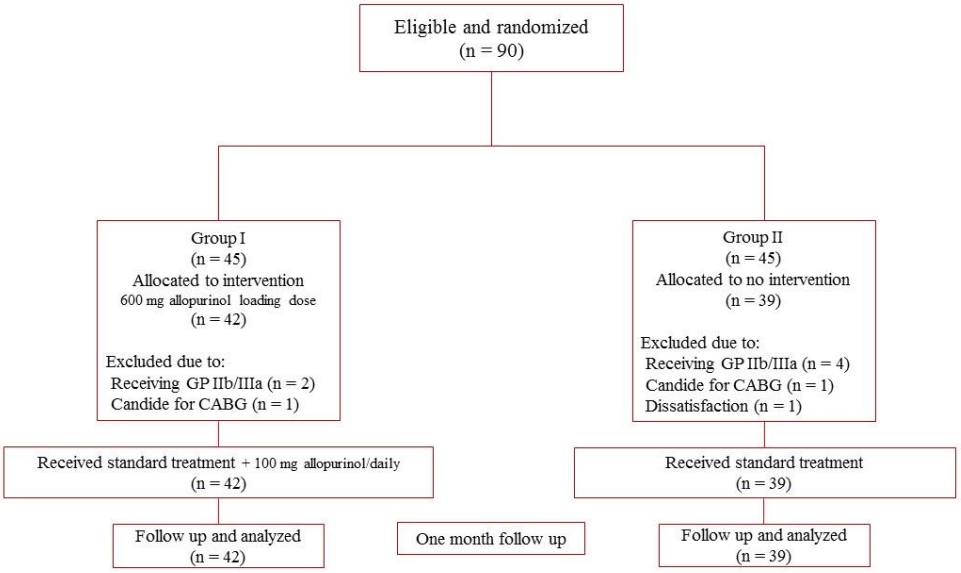

Figure 1. Study enrollment

Table 1. General characteristics of Allopurinol and placebo groups

	Allopurinol group (N=42)	Placebo group (N=39)	P-Value
Age (mean[SD])	59.52[11.31]	61.30[9.25]	0.49*
Gender (male) (%)	36(85.7)	32(82.1)	0.65**
History of DM (%)	9(21.4)	8(20.5)	0.91**
History of HTN (%)	18(42.9)	15(38.5)	0.68**
History of DLP (%)	12(28.6)	12(30.8)	0.82**
History of CVA (%)	1(2.4)	0	0.33¥
History of PCI (%)	4(9.5)	3(7.7)	0.95¥
Smoker (%)	18(42.9)	24(61.5)	0.09**
Hemoglobin(mg/dL) (mean[SD])	14.53[1.49]	14.93[1.61]	0.25*
Platelet (10^3/µL) (mean[SD])	219.65[56.96]	218.60[65.67]	0.51*
Creatinine (mg/dL) (mean[SD])	1.16[0.22]	1.09[0.23]	0.06α

*t-test ** Chi-Square ¥Fisher's Exact Test α Mann-Whitney
DM: diabetes mellitus, HTN: hypertension, DLP: dyslipidemia, CVA: cerebrovascular accident, PCI: percutaneous coronary intervention

The troponin level (ng/L) 48 hours after the PCI was 27581 (14129) in the allopurinol group and 31128 (13417) in the placebo group (p = 0.25). ECG ST-elevation regression also had no significant difference between the groups [75.0%1 vs 67.10% in the case and control groups, respectively (p = 0.21)]. TIMI flow had improved significantly in the allopurinol group rather than the placebo (p = 0.02). The PCI success rate was 78.6% and 61.5% in the allopurinol and control groups, respectively (p = 0.09) (Table 4). There was one mortality (2.4%) in the allopurinol group due to cardiac tamponade. MACEs and other clinical outcomes in the follow-up period were similar between groups (p > 0.05) (Table 5).

Table 2. Infarct characteristics of Allopurinol and placebo groups.

	Allopurinol group (N=42)	Placebo group (N=39)	P-Value
STEMI pattern (%)			
Anterior	4(9.5)	6(15.4)	
Antroseptal	6(14.3)	8(20.5)	
Lateral	0	1(2.6)	
Atrolateral	1(2.4)	2(5.1)	
Extensive	13(31)	5(12.8)	0.23¥
Inferior	7(16.7)	7(17.9)	
Posterior	0	3(7.7)	
Inferoposterior	7(16.7)	6(15.4)	
Inferioposteriolateral	1(2.4)	1(2.6)	
Inferior and RV	3(7.1)	0	
EF before PCI (mean[SD])	35.59[10.60]	38.20[7.11]	0.19*
Involve leads with STE (%)			
2 leads	0	3(7.7)	
3leads	11(26.2)	13(33.3)	
4leads	10(23.8)	12(30.8)	
5leads	7(16.7)	7(17.9)	0.14¥
6leads	12(28.6)	3(7.7)	
7leads	1(2.4)	0	
8leads	1(2.4)	1(2.6)	
Rescue PCI (%)	19(45.2)	14(35.9)	0.39**
Arrhythmia before PCI (%)			
No arrhythmia	34(81)	33(84.6)	
Sustained VT	1(2.4)	2(5.1)	
NSVT	3(7.1)	2(5.1)	
VF	1(2.4)	0	0.72¥
First degree AV block	1(2.4)	0	
CHB	1(2.4)	1(2.6)	
Bradycardia	0	1(2.6)	
AVRT	1(2.4)	0	

*t-test ** Chi-Square ¥Fisher's Exact Test

STEMI: ST elevation myocardial infarction, EF: Ejection fraction, PCI: percutaneous coronary intervention, STE: ST elevation, VT: ventricular tachycardia, NSVT: Non sustained ventricular tachycardia VF: ventricular fibrillation, AV: Atrio ventricular, CHB: complete heart block, AVRT: atrioventricular reentry tachycardia

Table 3. Angiographic and PCI characteristics of Allopurinol and control groups

	Allopurinol group (N=42)	Placebo group (N=39)	P-Value
Lesion length (mm) (mean[SD])	20.42[7.44]	20.05[5.27]	0.91*
Culprit vessel diameter (mm) (mean[SD])	2.98[0.34]	3.04[0.39]	0.25*
Stent length (mm) (mean[SD])	29.35[13.0]	34.70[17.92]	0.27*
Stent diameter (mm) (mean[SD])	3.01[0.34]	3.07[0.36]	0.31*

	Allopurinol group (N=42)	Placebo group (N=39)	P-Value
PCI artery (%)			
LAD	19(45.2)	19(48.7)	
LCX	2(4.8)	3(7.7)	
Diagonal	2(4.8)	1(2.6)	0.84**
RCA	12(28.6)	10(25.6)	
PDA	0	1(2.6)	
PLV	1(2.4)	0	
Multiple	6(14.3)	5(12.8)	
Diseased vessels (%)			
SVD	21(50)	17(43.6)	
2VD	13(31)	15(38.5)	0.91**
3VD	7(16.7)	6(15.4)	
LM	1(2.4)	1(2.6)	
TIMI before PCI (%)			
0	24(57.1)	25(64.1)	
1	4(9.5)	4(10.3)	0.54**
2	6(14.3)	3(7.7)	
3	8(19.0)	7(17.9)	
Lesion type (%)			
A	4(9.5)	3(7.7)	
B1	8(19)	9(23.1)	0.96**
B2	10(23.8)	9(23.1)	
C	20(47.6)	18(46.2)	
Stents type (DES) (%)	42(100)	37(94.9)	0.13**
Pre dilation (%)	36(85.7)	30(81.1)	0.57¥
Post dilation (%)	11(26.2)	12(32.4)	0.54¥

*Mann-Whitney **Fisher's Exact Test ¥Chi-Square
PCI: percutaneous coronary intervention, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, PDA: posterior descending artery, PLV: posterior left ventricular, SVD: single vessel disease, 2VD: two vessel disease, 3VD: three vessel disease, LM: left main, DES: drug eluted stents

Table 4. Post PCI outcomes between allopurinol and placebo groups

	Allopurinol group (N=42)	Placebo group (N=39)	P-Value
Troponin 48 hour after PCI (Median) ng/L (Q1-Q3)	33431 (16424.5-40000)	40000 (20320-40000)	0.133*
ST elevation regression (%) (mean[SD])	75.01[23.71]	67.10[33.32]	0.21
TIMI after PCI (%)			
≤1	0	5(12.9%)	
2	9(21.4%)	10(25.6%)	0.023**
3	33(78.6%)	24(61.5%)	
PCI success (%)	33(78.6%)	24(61.5%)	0.093

*Mann-Whitney test, **Cochran-Armitage test
PCI: percutaneous coronary intervention

Table 5. Post PCI clinically outcomes and MACEs.

	Allopurinol group (N=42)	Placebo group (N=39)	P-Value
Post PCI tamponade (%)	1(2.4)	0	0.519*
Arrhythmia (%)	3(7.1)	3(7.7)	0.626*
Stroke (%)	0	0	-
Death (%)	0	0	-
Stent thrombosis (%)	0	0	-
Recurrent Chest pain (%)	3(7.1)	3(7.7)	0.626*
Reinfarction (%)	0	0	-

*Fisher's exact test

PCI: percutaneous coronary intervention

Discussion

The result of this double-blind clinical trial indicated that allopurinol could improve coronary TIMI flow in patients admitted with acute STEMI who underwent primary or rescue PCI. Regarding other aspects of revascularization outcomes, including troponin level and ECG ST-elevation regression, there was no remarkable recovery in the allopurinol group.

According to scientific evidence, post-PCI coronary no-reflow phenomenon and TIMI flow grading depend on both inflammatory and coagulation pathways [13]; therefore, in addition to appropriate anticoagulants and platelet therapy, an anti-inflammatory therapeutic approach in patients with STEMI could be effective in reducing this phenomenon [14, 15]. Localization of ROS in the capillary endothelial cells and cell swelling in conjunction with activated neutrophils and aggregated platelets are inflammatory pathologies in the no-reflow phenomenon in STEMI patients undergoing emergency PCI [9]. As mentioned, allopurinol is expected to reduce inflammatory markers and oxidative stress by inhibiting the enzymatic pathway of xanthine oxidase, thereby improving the clinical outcome of patients [6-9]. In this regard, Guan et al. showed that for patients with STEMI pretreatment with 400 mg allopurinol (approximately 60 minutes before reperfusion) after PCI is useful in inhibiting the generation of oxygen-derived radicals during reperfusion therapy and the recovery of LV function in humans [9]. LVEF was not evaluated at follow-up in our study due to the short follow-up time (one month). The best time to assess LVEF is 3 to 6 months after the coronary intervention [9, 16]. Furthermore, the incidence of no-reflow or slow flow was decreased in this study as in our study. Rentoukas et al. demonstrated that allopurinol with a loading dose of 400 mg administered immediately after STEMI diagnosis and followed by a maintenance dose of 100 mg for 1 month, decreased peak troponin I, CK-MB and creatine kinase and ST-elevation recovery improved during hospitalization. Also, after a 1-month follow-up, patients in allopurinol-treated group had 13% fewer major adverse cardiac events [8]. Allopurinol did not reduce the incidence of cardiovascular events and complications in our study, which may have been due to timely PCI for all patients and perhaps due to the small sample size.

Unlike previous studies, in this study, allopurinol had no significant effect on lowering troponin levels. In fact, the highest rate of oxidative stress in acute myocardial infarction is 3 to 12 hours after the onset of symptoms, a time that has been selected in most studies to investigate the effect of allopurinol on inflammatory markers (1 and 3). In this study, because almost half of the patients underwent rescue PCI, the authors chose a time of 48 hours after the coronary

intervention to compare troponin levels, which may explain the negligible effect of allopurinol on troponin levels.

Limitations

This study had some limitations. The follow-up period of patients was short. Although, in the setting of emergency PCI, allopurinol had no effect on cardiac biomarkers, longer follow-up is necessary for long-term outcomes. Evaluation of serum levels of uric acid before and after the procedure could be suggested in future studies.

Conclusions

This study indicated that an allopurinol pre-treatment loading dose could improve coronary TIMI flow in the patients undergoing primary or rescue PCI in an acute STEMI setting.

Authors' Contributions

MKA and KHG designed and drafted the work. MKA, KHG, RG, MH and MS contributed to the interpretation of the data. HS, MKA, RG and KHG helped in the analysis of data. All authors performed the final revision.

Funding

None.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

The study protocol was approved by research ethics committees in School of Medicine - Isfahan University of Medical Sciences, Isfahan, Iran (approval ID: IR.MUI.MED.REC.1398.13 8) and was in accordance with the Declaration of Helsinki.

Consent to Participate

Written informed consent was obtained from all study participants.

Consent for Publication

Written informed consent was obtained from all study participants

Code Availability

All statistical analyses were generated with Statistical Package for Social Sciences (SPSS software (version 22, IBM Code Availability Armonk, NY, USA).

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