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The Effect of High-dose Allopurinol Pretreatment on Inflammatory Biomarkers and Post-revascularization Coronary Blood Flow in Non-STEMI Patients: A Randomized Double Blind Clinical Trial

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Original Article

Abstract

INTRODUCTION: The use of allopurinol has shown promising outcomes in reducing oxidative processes responsible for atherogenic-related cardiovascular events. The current study aims to assess the effects of high-dose allopurinol on the post-revascularization coronary blood flow and inflammatory biomarkers in patients with non-ST segment elevated myocardial infarction (NSTEMI).

METHOD: Eighty NSTEMI patients were randomly divided into two groups: the intervention group (n=40), medicated with a high loading dose of 600 mg allopurinol before the coronary angiography, and the control group (n=40), treated with a placebo. The highly sensitive C-reactive protein (hs-CRP) was measured at baseline and within 24 hours after the cardiac interventions and compared between the case and control groups. Post percutaneous coronary intervention (PCI) Thrombolysis in Myocardial Infarction (TIMI) flow grading was also evaluated as a revascularization endpoint.

RESULTS: The two groups of the study were similar in terms of demographic, clinical, laboratory, and angiographic characteristics (P-value>0.050). The assessed TIMI flow was similar between the cases and the controls both prior to (P-value=0.141) and after (P-value=0.395) the coronary angioplasty. The hs-CRP (P-value=0.016) was significantly higher in the control group. Post-angiographic assessment of hs-CRP revealed an insignificant difference between the groups (P-value=0.104).

CONCLUSION: In conclusion, premedication with a high dose of allopurinol in NSTEMI patients did not affect the inflammatory biomarker or the revascularization endpoint.

Keywords: Allopurinol, C-reactive protein, Non-ST elevated myocardial infarction, PCI

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Introduction

Cardiovascular events have become the leading cause of death worldwide, accounting for one-third of all annual deaths [1]. Accumulating evidence suggests that inflammatory processes are responsible for the incidence of cardiovascular events such as myocardial infarction. Indeed, reduced myocardial antioxidant activity and increased oxidative stress play a significant role in the pathogenesis

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of cardiac events. [2]

The overproduction of reactive oxygen species (ROS) can induce myocyte apoptosis [3]. One of the potential stimuli contributing to the progression of myocyte failure is the over-activation of xanthine oxidase, an enzyme responsible for the metabolism of purine, converting it to uric acid in the last two steps [4]. ROS, hydrogen peroxide, and superoxide ions are the components produced during these processes. In excess amounts, these may lead to reduced nitric oxide production. Decreased nitric oxide levels can cause endothelial dysfunction, characterized by vasoconstriction, increased thrombogenicity potential due to platelet activation, and smooth muscle proliferation; all of which are well-known for the pathogenesis and severity of myocardial infarction. [5-7]

Levels of xanthine oxidase are directly associated with circulating uric acid levels, which can indirectly reflect the level of oxidative stress. Although uric acid is a potent antioxidant agent, its high concentrations may promote oxidative stress in environments with low pH or low levels of other antioxidants [8].

Allopurinol, an inhibitor of xanthine oxidase, may effectively reduce the levels of oxidative agents and free radicals after their generation [9]. Both animal and human studies have shown promising outcomes with allopurinol against ischemia-reperfusion injury, including reduced infarction size, lower incidence of arrhythmia, improved ventricular function, and decreased release of myocardial creatine kinase [10-13]. However, the general use of allopurinol for patients with myocardial infarction (MI) remains a question due to insufficient data.

Therefore, this study aims, for the first time, to assess the effects of premedication with a high dose of allopurinol on coronary reperfusion in non-ST segment elevated myocardial infarction (NSTEMI) patients undergoing percutaneous coronary intervention (PCI). This is based on Thrombolysis in Myocardial Infarction (TIMI) flow grading. This goal could be crucial in improving TIMI flow grading and increasing successful PCI, which plays an inevitable role in post-MI left ventricle ejection fraction and infarction size. Additionally, the study investigates the pre-treatment effect of allopurinol on C-reactive protein (CRP) as a biomarker of inflammation.

Materials and Methods

Study population

The current double-blinded randomized clinical trial (RCT) was conducted on 80 patients admitted at Shahid Chamran Heart Center, affiliated with the Isfahan University of Medical Sciences, due to NSTEMI from May 2018 to June 2020.

The study protocol, which met the criteria of the Helsinki Declaration, was approved by the Ethics Committee of Isfahan University of Medical Sciences (approval ID: IR.MUI.MED.REC.1398.346). The study was also registered in the Iranian Registry of Clinical Trials with the code IRCT20191223045866N1. Participants were informed about the study protocol, reassured about the confidentiality of their information, and provided written consent.

Patients aged between 18 and 85 years, diagnosed with NSTEMI based on the World Health Organization (WHO) diagnostic definitions, and who expressed their willingness to participate in the study were included. NSTEMI was defined as typical chest pain or chest discomfort lasting more than 20 minutes in patients with positive cardiac biomarkers (troponin-I) but without ECG changes consistent with STEMI. [14]

Exclusion criteria included a previous medical history of allopurinol use, cardiogenic shock, level III and IV pulmonary edema, ventricular arrhythmia (including ventricular tachycardia and ventricular fibrillation), atrial fibrillation, and incidences of atrioventricular and sinoatrial node blocks before coronary catheterization.

Patients who met the inclusion criteria were included through convenience sampling and were then randomly divided into the intervention and control groups using Random Allocation software.

As the patients were blindly divided into two groups of "A" and "B", the cardiologist

responsible for treating them was blinded to the treatment groups.

Intervention

Both groups received routine medications for acute coronary syndrome (ACS), including 325 mg of acetylsalicylic acid, a 600 mg loading dose of Clopidogrel, and 80 mg Atorvastatin. In contrast, those allocated to group A were premedicated with a high loading dose of 600 mg allopurinol before undergoing coronary angiography. The remaining participants in group B received a placebo, similar in shape, color, and size to allopurinol, made by the Isfahan Pharmacy faculty, Isfahan University of Medical Sciences, Isfahan, Iran.

If indicated, coronary intervention included balloon angioplasty and drug-eluting stents (DES) implantation. The aim was to achieve angiographic success, defined as residual stenosis less than 20% in the presence of grade 3 TIMI flow without major intimal dissection. The requirement of glycoprotein (GP) IIb/IIIa inhibitors injections for procedure performance was considered a confounding factor and thus an exclusion criterion.

Outcomes

The main endpoints of the current study were to assess the alterations in the quantitative levels of highly sensitive C-reactive protein (hs-CRP) as the biomarker representing the intensity of inflammation. These measurements were done at baseline immediately when the patient was referred to the hospital and repeated within 24 hours after coronary angiography with or without angioplasty. In patients undergoing intervention, TIMI flow grading was also evaluated before and after the PCI. The patients were monitored for the incidence of recurrent chest pain and the occurrence of major adverse cardiac events (MACEs) as well as ventricular and supra-ventricular arrhythmia.

In addition to the previous data, the patients' left ventricular ejection fraction at discharge, the approach taken to treat the patients (medical treatment, coronary artery bypass grafting (CABG), and PCI), and angiographic findings (number(s) of involved epicardial territories, length of the lesions, the diameter of the involved vessels, and types of the lesion) were recorded.

Other obtained data included demographic and habitual information (age, gender, and smoking), past medical history (diabetes mellitus, hypertension, previous history of ischemic heart disease, chronic kidney diseases, dyslipidemia, congestive heart failure), and laboratory evaluations (complete blood count, urea, and creatinine).

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (version 22, IBM Corporation, Armonk, NY, USA). The descriptive data were presented as mean, standard deviation, absolute numbers, and percentages. The chi-square test was utilized to compare the frequencies between the groups. The t-test was used to compare continuous variables. Due to the non-normal distribution of hs-CRP and its wide ranges, the logarithm of these variables was administered in Table 3. The ANCOVA test was applied to control the confounding variable. In addition, to assess the probable confounding role of demographic characteristics, in addition to assessing the association of these factors with the independent variable, their association with dependent ones was evaluated. A P-value of less than 0.05 was considered as a significant level.

Results

In this study, 80 patients with NSTEMI symptoms were assessed in two groups: one premedicated with a high dose of allopurinol (intervention group) and the other with a placebo (control group). All 80 patients who met the inclusion criteria completed the study protocol (Figure 1).

The demographic, clinical, and laboratory characteristics of the studied population showed no significant differences (P-value>0.050), except for smoking (P-value=0.014), platelet count (P-value=0.016), and creatinine (P-value=0.019). Detailed information is presented in Table 1.

Table 2 shows the characteristics related to the angiography/angioplasty performed for the patients. The two groups were

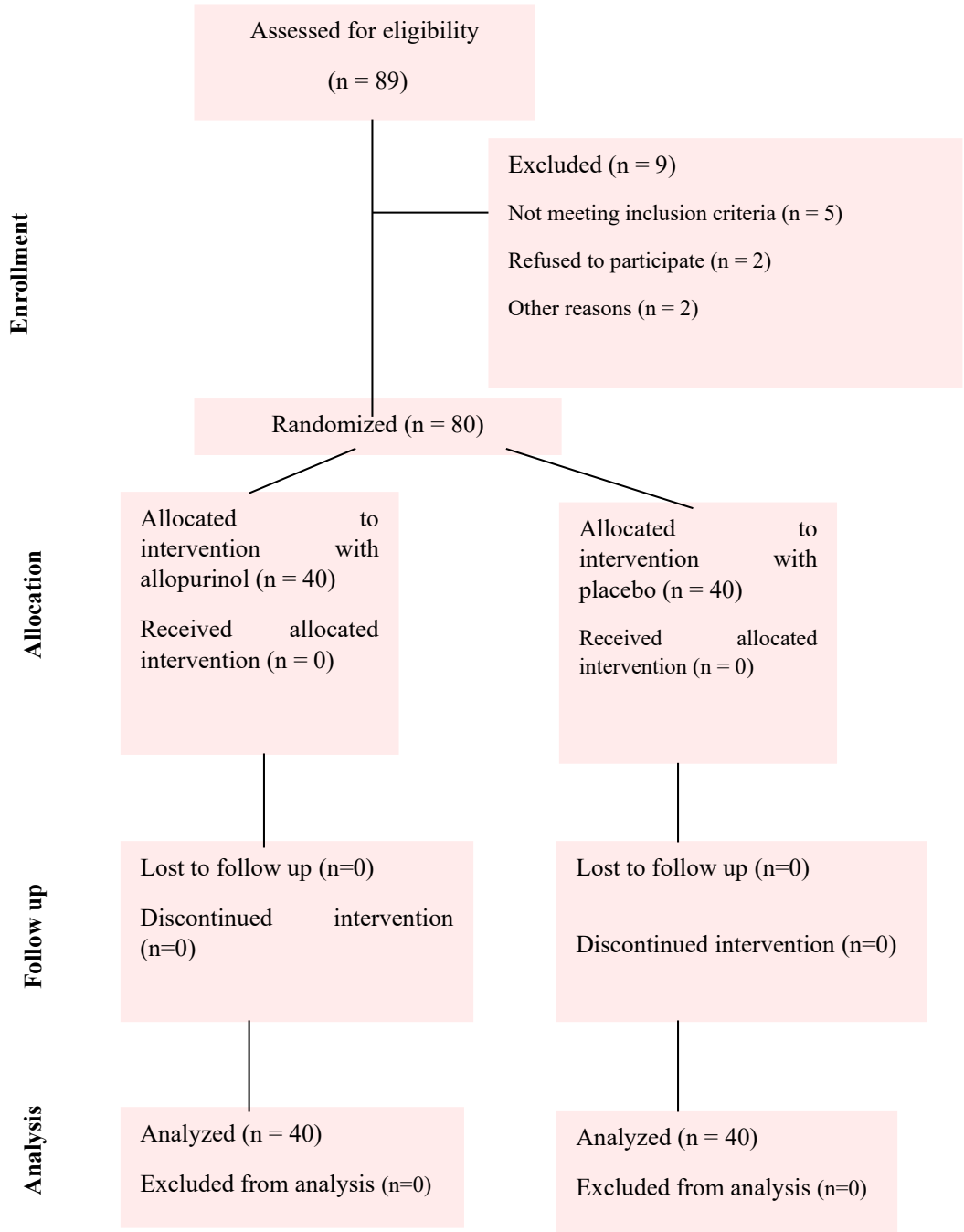

Figure 1. Consort diagram of the studied population

similar in terms of the number of involved epicardial coronary artery territories, the treatment approach used, lesion length, vessel diameter, and type of lesion (P-value>0.050). Furthermore, the incidence of recurrent chest pain (6 versus 3 in the allopurinol and control group, respectively; P-value=0.288) and the incidence of arrhythmia (5 versus 7 in the allopurinol and control group, respectively; P-value=0.531) were similar between the groups. Premature ventricular contraction was the only major arrhythmia observed during monitoring.

Table1. The comparison of demographic, clinical, and laboratory characteristics between the intervention and control groups

Variable	Total	Intervention	Control	P-value
Age	61.4±10.74	60.03±10.02	62.78±11.37	0.225*
Sex				
Male	57(71.3)	28(70.0)	29(72.5)	0.805**
Female	23(28.8)	12(30.0)	11(27.5)	
Diabetes mellitus	31(38.8)	18(45.0)	13(32.5)	0.251**
Hypertension	40(50.0)	18(45.0)	22(55.0)	0.371**
Ischemic heart disease	26(32.5)	11(27.5)	15(37.5)	0.34**
Chronic kidney disease	5(6.3)	2(5.0)	3(7.5)	0.644**
Dyslipidemia	16(20.0)	11(27.5)	5(12.5)	0.094**
Congestive heart failure	1(1.3)	1(2.5)	0(0)	0.314**
Smoking	17(21.3)	13(32.5)	4(10.0)	0.014**
White blood cell count (per ml)	9180.1±9223.9	9712±12752.9	8648.25±3020.41	0.609*
Hemoglobin (g/dl)	14.47±1.89	14.22±2.01	14.72±1.74	0.241*
Platelet count (per ml)	207705.2±80497.58	186255.2±75315.9	229155.2±80681.9	0.016*
Urea (mg/dl)	38.2±12.55	36.85±13.23	39.55±11.83	0.339*
Creatinine (mg/dl)	1.13±0.225	1.07±0.197	1.19±0.239	0.019*
Left ventricular ejection fraction (%)	46.06±9.30	46.38±9.06	45.75±9.64	0.766*
Left ventricular ejection fraction				
< 30	8(10.0)	4(10.0)	4(10.0)	0.918
30 – 40	15(18.8)	8(53.3)	7(17.5)	
40 – 50	35(43.8)	16(40.0)	19(47.5)	
≥ 50	22(27.5)	12(30.0)	10(25.0)	

*Data are shown as mean±SD. An independent sample t-test was used.

**data are shown as N(%). A Chi-square test was done

Table 2. The comparison of angiographic/angioplasty related characteristics between the intervention and control groups

Variable	Intervention	Control	P-value
Angiographic findings (%)			0.213**
1VD	14(35.0)	6(15.0)	
2VD	11(27.5)	13(32.5)	
3VD/LM	13(32.5)	19(47.5)	
Minimal CAD	2(5.0)	2(5.0)	
Intervention type			0.073**
Medical treatment or CABG	15(37.5)	23(57.5)	
PCI	25(62.5)	17(42.5)	
Lesions Length	20.0±12.79	15.41±6.51	0.135*
Vessels diameter	2.92±0.589	2.91±0.414	0.961*
Type of the Lesion			0.274**
A	4(16.0)	5(29.4)	
B1	9(36.0)	7(41.2)	
B2	1(4.0)	2(11.8)	
C	11(44.0)	3(17.6)	
Pre dilation (%)	24(96.0)	15(88.2)	0.338**
Post dilation (%)	5(20.0)	1(5.9)	0.199**
Successful PCI Result (%)	22(88.0)	13(76.5)	0.325**

Variable	Intervention	Control	P-value
TIMI score before the intervention			0.141**
0	6(24.0)	5(29.4)	
1	0(0)	3(17.6)	
2	12(48.0)	5(29.4)	
3	7(28.0)	4(23.5)	
TIMI score after the intervention			0.395**
0	0(0)	1(5.9)	
1	0(0)	0(0)	
2	3(12)	3(17.6)	
3	22(88)	13(76.5)	

*Data are shown as mean±SD. An independent sample t-test was used.
**data are shown as N(%). A Chi-square test was done
1VD: one vessel disease, 2VD: two vessels disease, 3VD: three vessels disease, LM: left main artery, CAD: coronary artery disease, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, TIMI score: the thrombolysis in myocardial infarction score

Assessments of TIMI flow grading as the revascularization endpoint of this study revealed no significant difference between the cases and controls both prior to (P-value=0.141) and after (P-value=0.395) the PCI (Table 2). The baseline hs-CRP (P-value=0.016) was significantly lower in the intervention group compared to the controls. The follow-up assessment of adjusted hs-CRP revealed no statistically significant difference between the cases and the controls (P-value=0.104).
Regarding the side effects of allopurinol, although skin rash and gastrointestinal disorders such as nausea and diarrhea are more common side effects, none of the patients reported them.

Table 3. The comparison of hs-CRP changes between the intervention and control groups

Variables	Group	Before Ln (Mean±SD)	After Ln (Mean±SD)	p-value****
hs-CRP	Intervention	1.64 ± 0.24	2.44 ± 0.70	<0.001
	Control	2.20 ± 0.24	2.52 ± 0.70	0.004
	P-value	0.016*	0.104β	

*adjusted for Plt, Cr and Smoking
β adjusted for Plt, Cr, Smoking and hsCRP (before)
***Paired Sample test
hs-CRP: highly sensitive C-reactive protein, plt: platelet, Cr: creatinine

Discussion

To the best of our knowledge, this is the first study on NSTEMI patients assessing the effects of premedication with allopurinol on hs-CRP as a marker of inflammation and revascularization outcomes. The studied groups were similar in terms of demographic, medical history, laboratory, and angiographic data, so the results can be attributed solely to the premedication regimen. We found that the levels of hs-CRP, representing inflammation,

did not differ between the groups following the interventions. Also, premedication with a high dose of allopurinol did not affect TIMI flow grading as the revascularization-related endpoint. However, for the generalization of our findings, further studies are required.

An increase in free radicals due to reperfusion by PCI, known as reperfusion injury, has been noted. Further studies in this area have presented controversial outcomes. Alemzadeh-Ansari and colleagues found no benefit in premedication with a high loading dose of 600 mg allopurinol in cardiac biomarkers of the patients undergoing elective PCI [15]. Similar outcomes were achieved by Huang et al. in early assessments, while by only the next month, the inflammatory biomarkers serum levels were considerably lower among those with acute coronary syndrome who administered allopurinol [16]. In contrast, Rentoukas et al. administered 400 mg allopurinol immediately after STEMI incidence, followed by a 100 mg daily dose for a month, and reported a remarkable decrease in cardiac biomarkers and MACE incidence [10]. Another study by Guan et al., who used a 400 mg loading dose of allopurinol within 60 minutes before PCI on patients with STEMI, reported a significant decrease in free-radical levels during reperfusion therapy and a remarkable improvement in left ventricular function [17]. Ekeløf and colleagues also reported promising data in this regard [18].

Allopurinol, a xanthine oxidase inhibitor, has been used for a long time to treat gout. However, evidence in the literature has shown promising data for its use due to anti-ischemic properties among patients with angina pectoris [19]. Studies suggest that xanthine oxidase inhibition leads to a considerable reduction in myocardium oxygen consumption for a particular stroke volume [20]. A ten-year follow-up study on patients with hypertension as a cardiac risk factor showed remarkable improvement in blood pressure control [21]. Similar positive outcomes in favor of xanthine oxidase inhibition were achieved assessing cardiac function determinants, including cardiac index, left ventricular ejection fraction (LVEF), and cardiac efficiency [22].

Another aspect that reinforced the theory about using this agent is the studies insisting on the antioxidant nature of allopurinol that can reduce endothelial dysfunction. These data have been achieved through animal and human studies conducted on patients with diabetes mellitus, hypertension, smokers, obstructive sleep apnea, and coronary artery diseases [23-25]. Nevertheless, most of the beneficial outcomes were presented among hyperuricemic cases; because hyperuricemia reflects pathological enzyme activity [26]. On the other hand, most of the trials on healthy subjects did not show significant benefits. It seems that xanthine oxidase has a limited role in determining endothelial function in a healthy vascular system. In addition, evidence suggests that stresses such as ischemia are responsible for enzyme activity [27].

Kanbay et al. conducted a study to assess the efficacy of allopurinol therapy on the patients' renal function and utilized CRP as the determinant of chronic inflammation. They presented remarkable renal function improvement, creatinine clearance, and reduction in CRP [28]; however, numerous other studies did not reproduce similar outcomes [29, 30]. What was mentioned above insisted on the long-term use of allopurinol to reduce xanthine oxidase levels permanently. However, the current study and limited other ones have investigated the impact of this agent's high loading dose on the inflammatory and cardiac biomarkers following an acute ischemic event. It has been demonstrated that allopurinol can reduce the infarction size, improve cardiac function and reduce the risk of arrhythmia incidence [31, 32]. Even, Miwa-Nishimura presented the reduced release of myocardial creatine kinase [11]. In this study, post PCI Thrombolysis in Myocardial Infarction flow and PCI success rate was also insignificantly better in the allopurinol group.

The studies favoring high loading doses of allopurinol present that xanthine oxidase as the major ROS source in the vascular system leads to a burst of free radicals generation when ischemia occurs. Therefore, this enzyme's overproduction deteriorates

vascular oxidative stress and decreases vascular vasodilatory capability by limitation in nitric-oxide activity during ischemia [33, 34].

The timeline determined for the re-measurement of biomarkers in this study is assumed to be a crucial factor associated with the outcomes opposing the effectiveness of high-dose allopurinol premedication to minimize ischemic-related consequences. For instance, CRP, a marker of inflammation, is an acute phase protein produced by the liver and reaches its maximal level within 72 hours [35]. This fact may reflect the reason for the elevation of CRP in the follow-up assessments and the logic of the insignificant difference between the case and control group.

The most significant limitation of this study is the reassessment of hs-CRP levels within only 24 hours after the first measurement, which seems inadequate to draw a conclusion for routine high-dose allopurinol administration. Another limitation is the failure to present the interval between myocardial infarction incidence and the measurement of biomarkers, a factor that may impact serum levels of troponin-I and hs-CRP. The small number of the studied population and the failure to follow the patients in a short-term period to find the in-hospital adverse events and MACEs are other factors representing the necessity of further investigations.

Conclusion

Based on the findings of this study, premedication with a high dose of allopurinol in NSTEMI patients did not affect hs-CRP, the inflammatory biomarker, as well as revascularization endpoints according to TIMI flow. Further long-term studies on more extended biomarkers are strongly recommended.

Data availability

All data analyzed during this study are included in this article and available from the corresponding author upon request.

Conflict of interest

The authors declare that they have no conflicts of interest.

Authors contribution

M. KA, K. HG and A. A were involved in conception. H. S, M. KA, K. HG and M. S were responsible for design. A. A, A. S, M. KA carried out data acquisition. All authors conducted data interpretation. K. HG, M. KA and A. S analyzed data. All authors drafted and revised the manuscript and finally approved the manuscript.

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