DOI: http://dx.doi.org/10.48305/arya.v18i0.2681 Published by Vesnu Publications

The effect of heparin administration time on thrombolysis in myocardial infarction flow grade in patients with acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention

Aboozar Fakhr-Mousavi MD[1], Shaghayegh Cheshmkhorooshan MD[2], Azin Vakilpour MD[3], Seyed Mehdi Mousavi MD[1]

Original Article

Abstract

BACKGROUND: In the clinical setting of patients with ST-elevation myocardial infarction (STEMI), there are controversies about the role of early heparin administration on the patients' outcome and the patency of the infarct-related artery (IRA). In this randomized clinical trial, we sought to investigate the effect of heparin administration time on the thrombolysis in myocardial infarction (TIMI) flow grade of patients with STEMI treated with primary percutaneous coronary intervention (PPCI).

METHODS: Eligible individuals were randomly assigned to two groups: early heparin administration (90 IU/kg) in the emergency department (group A, n = 92) and late heparin administration in the Cath lab (group B, n = 77). All demographic and clinical information and on admission examinations were documented. Clinical outcomes, 40-day mortality, and left ventricular (LV) function improvement in follow-up were also collected.

RESULTS: The mean age of patients was 57.1 ± 8.8 and 57.5 ± 7.5 years in groups A and B, respectively (P = 0.232). The history of hypertension (HTN) (34.8% vs. 53.2%, P = 0.016) and diabetes (14.1% vs. 29.9%, P = 0.013) was significantly lower in group A. The LV ejection fraction (LVEF) changes were significant before and after the intervention within each group. However, this change was not significantly different between the groups (P = 0.592). Post-intervention complications did not differ between the two groups (P > 0.05). In the proportion of cases with TIMI flow grade less than 2 in the IRA, no significant differences were observed between the groups. [P = 0.092 for left anterior descending (LAD) and P = 0.086 for left circumflex artery (LCX)].

CONCLUSION: Although heparin administration in patients with STEMI undergoing PPCI is safe and effective, the effect appears not to be time-dependent.

Keywords: Angioplasty; Heparin; Myocardial Infarction; ST-Elevation Myocardial Infarction; Thrombolysis

Date of submission: 06 Nov. 2021, ***Date of acceptance:*** 20 Dec. 2021

Introduction

Myocardial infarction (MI) is a cardiac emergency in which the patient may die or suffer from the complications of the disease if emergency medical care is not provided in the golden time.[1]

ST-segment elevation MI (STEMI) resulting from thrombotic occlusion of a coronary artery overlaid on a ruptured atherosclerotic plaque is one of the leading causes of mortality and morbidity worldwide.[2,3]

How to cite this article: Fakhr-Mousavi A, Cheshmkhorooshan S, Vakilpour A, Mousavi SM. **The effect of heparin administration time on thrombolysis in myocardial infarction flow grade in patients with acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention.** ARYA Atheroscler 2022; 18: 2681.

1- Assistant Professor, Cardiovascular Diseases Research Center AND Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
2- Cardiologist, Cardiovascular Diseases Research Center AND Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
3- General Practitioner, Cardiovascular Diseases Research Center AND Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
Address for correspondence: Seyed Mehdi Mousavi; Assistant Professor, Cardiovascular Diseases Research Center AND Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
Email: dr.smmousavi.md@gmail.com

The primary goal of the initial treatment in MI is early coronary reperfusion.[4] The ideal reperfusion strategy in patients with STEMI is primary percutaneous coronary intervention (PPCI), mainly when performed in the first 2 hours following diagnosis.[5,6] Primary angioplasty may result in a more inclusive and steady patency rate of the infarct-related artery (IRA) compared with thrombolytic therapy.[7] In angiography, blood flow in IRA is evaluated by a simple qualitative system called the thrombolysis in myocardial infarction (TIMI) risk score. In this system, zero degree means complete occlusion of the artery, grade 1 means that there is a little blood flow, while blood flow does not reach the coronary arteries that are distal to the site of obstruction, grade 2 is a sign of normal blood flow in the infarct artery, but blood flow is delayed compared to a normal artery, and grade 3 indicates complete blood supply to the infarct vessel with normal blood flow. The goal of treatment is to re-establish grade 3 flow.[8] Nevertheless, an increased time between admission and the initiation of the treatment is one of the drawbacks of primary angioplasty, especially when the patient is admitted to general hospitals and then referred to a specialized angioplasty center. The delay between the beginning of symptoms and reperfusion of the IRA is associated with poor outcomes.[9] Adjunctive therapy would be invaluable when given in the delay period before angioplasty. Reperfusion may be induced by adjunctive therapy and limit myocardial injury.[10] Intravenous (IV) unfractionated heparin (UFH) (a heterogeneous mixture of polysaccharide molecules) has been found to be efficient in early thrombin activity and occlusion reduction, and improves the culprit artery patency.[11,12]

In addition, it is a well-known procedure for anticoagulant therapy at the time of percutaneous coronary intervention (PCI) in patients with STEMI.[13] Heparin is an anticoagulant agent that inactivates thrombin and factor Xa through activating the antithrombin III in body, and eventually inhibits clot formation.[14] Heparin is mainly useful to prevent and treat venous thromboembolism (VTE) and pulmonary embolism (PE), reduce the risk of molar thrombosis after MI, and treat patients presenting with unstable angina and MI.[15] UFH binds strongly to plasma proteins which results in unpredictable levels of free heparin in the blood circulation. Thus, UFH presents significant alterations in antithrombotic results and needs close monitoring.[12]

However, in the clinical setting of patients with acute STEMI, there are some controversies about the role of early heparin administration time on the patients' outcome and the culprit vessel patency. Hence, we tried to evaluate the findings of previous papers in a randomized clinical trial by investigating the effect of heparin administration time (early administration in the emergency department compared to administration in the Cath lab) on the TIMI flow grade and short-term outcomes in patients with STEMI.

Materials and Methods

The present randomized clinical trial was performed on all patients with STEMI who were referred to Heshmat Cardiovascular Hospital, the only referral cardiology center of Guilan Province, Rasht, Iran, and were treated with PPCI from May to August 2020.

Patients with chest pain onset within the previous 12 hours and electrocardiographic (ECG) changes with ST-elevation more than 1 mm in at least two adjacent leads, the occurrence of pathological Q waves, or new left bundle branch block (LBBB) were enrolled. Exclusion criteria included patients who voluntarily left the hospital or were transferred to another center for any reason. In addition, patients who had received antithrombotic drugs in the last seven days, pregnant women, those with active bleeding, a history of heparin-induced thrombocytopenia (HIT), pre-hospital heparin intake, a history of thrombocytopenia and coronary artery bypass graft (CABG) surgery as well as patients aged over 75 years and those with the previous history of failed PCI were excluded.

After obtaining written informed consent to participate, eligible individuals were randomly assigned to two groups: early heparin administration group in the emergency department (group A, intervention group) and late heparin administration group in the Cath lab (group B, control group). Heparin administration in the emergency room was decided by the cardiologist on duty. This trial was carried out according to the Declaration of Helsinki, and the study procedure was approved by the Ethics Committee of Guilan University of Medical Sciences with the code number of IR.GUMS.REC.1399.056. Besides, the trial was registered to the clinical trial registration system with Iranian Registry of Clinical Trials (IRCT) registration number of IRCT20170925036401N2.

STEMI diagnosis was performed based on

clinical symptoms as typical cardiac chest pain and ECG changes (ST-elevation more than 1 mm in at least two adjacent leads, the occurrence of pathological Q waves, or new LBBB). As soon as STEMI was diagnosed, the patient was transferred to the Cath lab and underwent PPCI. Patients in group A received IV heparin as soon as they arrived in the emergency room and were diagnosed with STEMI. IV injection of UFH 90 IU/kg was performed according to the guidelines (5000 units were injected stat IV in the emergency department, and the rest was administered based on the weight in the Cath lab).[16-18] Patients in group B received 90 IU/kg of heparin in the Cath lab during angiography. Moreover, 325 mg of aspirin and 600 mg of clopidogrel were administrated to the patients in the emergency room.

Data on demographic information, clinical data such as previous medical history, the time interval from the onset of pain to being referred to the emergency unit, on admission examinations, MI characteristics, ejection fraction (EF) on arrival, and Killip class were extracted from the patients' files. Angiography and angioplasty information, including identifiable culprit vessel and vascular access during angiography and post-intervention complications [thrombosis, hemorrhage, and hematoma at the site of angiography, ventricular tachyarrhythmia, ventricular tachycardia (VT), ventricular fibrillation (VF), flail mitral valve (MV), free wall rupture, pericardial effusion, and in-hospital death] were also gathered. Patency of the IRA was scored based on the TIMI flow grade. All the angiographic data were interpreted by 2 independent cardiologists blinded to the heparin administration time. Related post-discharge information, including 40-day mortality and left ventricular (LV) function improvement assessed by transthoracic echocardiography (TTE), were also collected forty days after discharge.

Statistical analysis: Continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as number (percentage). A chi-square test or Fisher's exact test was applied to determine the relationship between two categorical variables. Kolmogorov-Smirnov test was used for testing normality assumption. To compare one quantitative variable in two independent groups, an independent t-test or Mann-Whitney U was utilized. Wilcoxon signed-rank test was applied to compare changes within each group. SPSS software (version 22, IBM Corporation, Armonk, NY, USA) was used to analyze the data. The level of significance was set at 0.05.

Results

Data from 169 patients with STEMI in the intervention and control groups were analyzed. In group A, 92 individuals (54.4%) and in the control group, 77 patients (45.6%) were included. The mean ± SD of age in groups A and B was 57.1 ± 8.8 and 57.5 ± 7.5 years, respectively. There was no significant difference in terms of age between groups (P = 0.232). A total of 72 cases (78.3%) in group A were men. In group B, 60 men (77.9%) and 17 women (22.1%) were included. There was no significant difference in terms of sex between groups (P = 0.958). The data on previous clinical history are presented in table 1.

Table 1. Baseline characteristics of patients with ST-elevation myocardial infarction (STEMI) receiving early heparin treatment in the emergency departments (group A) and patients who received heparin in catheterization lab (group B)

Parameter	Group A (n = 92)	Group B (n = 77)	P
Male gender	72 (78.3)	60 (77.9)	0.958*
HTN	32 (34.8)	41 (53.2)	0.016*
Diabetes	13 (14.1)	23 (29.9)	0.013*
Dyslipidemia	19 (20.7)	24 (31.2)	0.118*
History of CVA	2 (2.2)	1 (1.3)	0.668**
Family history of SCD	24 (26.1)	20 (26.0)	0.987*
Killip class			
I	89 (96.7)	75 (97.4)	
II	2 (2.2)	2 (2.6)	0.988**
III	1 (1.1)	-	
Age (year)	57.1 ± 8.8	57.5 ± 7.5	0.232***

Data are presented as mean ± standard deviation (SD) for continuous variables and absolute number (percent) for categorical variables

*Results from chi-square test; **Results from Fisher's exact test; ***Results from independent samples t-test

HTN: Hypertension; CVA: Cerebrovascular accident; SCD: Sudden cardiac death

The history of hypertension (HTN) and diabetes was significantly lower in group A (P = 0.016 and P = 0.013, respectively). The mean ± SD of pain period (accurate MI onset time) was 334.0 ± 176.1 and 308.0 ± 156.9 minutes in groups A and B, respectively, with no significant difference between groups (P = 0.315).

Based on the results of angiography and angioplasty, an identifiable culprit vessel with femoral access was present in all patients of both groups. Mechanical thrombectomy was not used for any of the participants. Those patients with STEMI in both groups who had no reflow in angiography received glycoprotein IIb/IIIa (GPIIb/IIIa).

The degree of TIMI flow was not significantly different between the two groups. In the classification of TIMI flow grade (less than 2 and more than 2), no significant difference was observed [P = 0.092 and P = 0.086 for left anterior descending (LAD) and left circumflex artery (LCX), respectively]. Angiographic thrombus burden based on TIMI grading is presented in table 2. Regarding post dilation approach, Plain Old Balloon Angioplasty (POBA) was used for post dilation after stent placement in 5 patients (5.4%) in group A and 5 patients (6.5%) in group B.

Post-intervention complications were not significant between the two groups (P > 0.05). One person in both groups experienced recurrent MI (P = 0.988). Three patients in both control and intervention groups showed ventricular tachyarrhythmia (P = 0.682). Supraventricular tachyarrhythmia was detected in 1 patient of group B (P = 0.988). One patient in group A and 2 patients in group B showed bradyarrhythmia after intervention (P = 0.988). Mechanical complications such as flail MV, free wall rupture, ischemic and hemorrhagic stroke, stent thrombosis, bleeding, hematoma formation of the angiographic site, and in-hospital mortality were detected in neither group. Besides, the Killip class was not significantly different among groups [class I: group A: n = 89 (96.7%), group B: n = 75 (97.4%); class II: group A: n = 2 (2.2%), group B: n = 2 (2.6%)] (P = 0.988). Comparing the types of MI, the prevalence of inferior wall MI was significantly higher in group A compared to group B (P = 0.02) (Table 3).

The left ventricular ejection fraction (LVEF) has increased significantly after intervention in both groups (mean of LVEF at admission: 35%, and after 40 days: 41%) (P = 0.001 in group A, and P ≤ 0.001 in group B). LVEF increased 40 days after PPCI in both groups, but according to the Mann-Whitney test, LVEF changes were not statistically different between the two groups (P = 0.592) (Table 4).

Discussion

Regional networks have been formed to develop STEMI patients' care by reducing delays in restoring blood flow and improving reperfusion.[19,20] Even with the formation of regional networks such as the Acute Myocardial Infarction Code network (AMI Code) established in Catalonia, Spain, in 2009, some delays still exist in patients' transfer to the Cath lab.[21] Patients exposed to long delays can benefit from any treatment given during that time to improve IRA patency before PPCI.

Table 2. Thrombolysis in myocardial infarction (TIMI) flow grade of the culprit vessel before and after intervention in group A (early heparin administration in the emergency room) and group B (heparin administration in catheterization lab)

		TIMI grade in group A (n = 92)				TIMI grade in group B (n = 77)				P*
		0	1	2	3	0	1	2	3	
LAD	Before	36	6	8	1	41	11	3	1	0.247
	After	0	0	2	49	0	0	2	54	0.988
LCX	Before	6	0	0	0	3	1	1	0	0.182
	After	0	0	0	6	0	0	1	4	-
OM	Before	4	0	0	0	3	0	0	0	0.437
	After	0	0	1	3	0	0	0	3	-
Diagonal	Before	0	0	0	0	0	0	1	0	-
	After	0	0	0	0	0	0	0	1	-
RCA	Before	22	6	0	0	10	2	0	0	0.738
	After	0	0	0	28	0	0	0	12	-

Data are presented as absolute number

*Results from Fisher's exact test

TIMI: Thrombolysis in myocardial infarction; LAD: Left anterior descending artery; LCX: Left circumflex artery; OM: Obtuse marginal; RCA: Right coronary artery

Note: It was not possible to estimate P-value for LM, diagonal, OM, and PDA

Table 3. The prevalence of myocardial infarction (MI) in different cardiac walls in group A (early heparin administration in the emergency room) and group B (heparin administration in catheterization lab)

	Group A	Group B	P
High lateral	5 (5.4)	7 (9.1)	0.384*
Anterior	45 (48.9)	40 (51.9)	0.694*
Extensive anterolateral	6 (6.5)	11 (14.3)	0.095*
Inferior	37 (40.2)	18 (23.4)	0.020*
Posterior	14 (15.2)	7 (9.1)	0.229*
RV	9 (9.8)	3 (3.9)	0.228**
Septal	-	1 (1.3)	0.456**
LBBB	1 (1.1)	-	0.988**

Data are presented as absolute number (percent)
*Chi-square test; **Fisher's exact test
RV: Right ventricle; LBBB: Left bundle branch block

Present guidelines recommend adjunctive antithrombotic treatment with antiplatelet and anticoagulant medications before PPCI in patients diagnosed with STEMI, but the ideal administration timing is still controversial.[11]

The present clinical trial highlights the positive effects of heparin in patients with STEMI. Post-intervention complications such as flail MV, free wall rupture, ischemic and hemorrhagic stroke, stent thrombosis, bleeding, and hematoma formation of the angiographic site were not detected in both control and intervention groups. TIMI flow information was not significantly different between the two groups, and it was assumed that high-dose heparin administration before primary angioplasty as a safe method was not associated with a greater rate of IRA patency. Moreover, the LVEF significantly increased in both groups following intervention and in the 40-day follow-up; however, the effect of anticoagulant therapy with UFH in patients with STEMI undergoing PPCI appeared not to be time-dependent.

Previous research on the effect of heparin on IRA patency provided inconsistent results. In a recent investigation on a small sample of patients, heparin administration in the emergency department before the transfer of the patient to the Cath lab showed no significant relationship with vessel patency upon initial angiogram.[22] Our findings are also partly compatible with McGinley et al. study, investigating the impact of pre-hospital treatment with UFH in patients with STEMI on the long-term survival, which demonstrated that pre-hospital heparin administration was significantly in association with improved long-term survival, albeit they could not support that early heparin administration could improve early coronary patency.[3] Zamani et al. suggested that PPCI resulted in a satisfactory coronary flow regardless of receiving bolus heparin in patients with STEMI.[23]

On the contrary, Bloom et al. in 2021 found that pre-hospital UFH administration was significantly associated with improved patency of occulted artery. They reported that pre-hospital heparin use was strongly associated with anterograde flow in the IRA, and similar to our findings, did not enhance the risk of major bleeding.[13] Chung et al. assessing the effect of heparin therapy in the emergency department compared to it at the time of catheterization on 130 patients with STEMI showed that early heparin administration prior to Cath lab was associated with more favorable TIMI flow grade at the angiography.[24] Additionally, in another recent study, administration of UFH improved coronary reperfusion in patients with STEMI before PPCI, which may be associated with superior clinical outcomes.[11]

In Zamani et al. study, clinical outcome, 30-day mortality, hematoma incidence, and LV function improvement during follow-up were compared between the two groups. The results of their study showed that in both groups, appropriate vessel flow was established following PCI.[23] Compatible with our finding, they revealed that receiving bolus heparin might improve LV function with no increased rate of bleeding and mortality in 30-day follow up.[23] In the Giralt et al. investigation in 2020, the rate of bleeding in which patients needed blood transfusion was very low, with no differences between groups. [11]

Table 4. Mean percentage of ejection fraction (EF) changes in patients with acute myocardial infarction (MI) in group A (early heparin administration in the emergency room) and group B (heparin administration in catheterization lab)

EF	Group A		Group B		P*
	Mean ± SD	Median	Mean ± SD	Median	
Initial	35.0 ± 9.1	35	35.0 ± 8.0	35	0.743
After 40 days	41.0 ± 10.8	42	41.0 ± 11.0	42	0.592
P-values of changes**	< 0.001		0.001		

*Inter-group, Mann-Whitney U test; **Intra-group, Wilcoxon signed-rank test
EF: Ejection fraction; SD: Standard deviation

Moreover, in the study by Chung et al., no significant differences were found in 2 groups regarding TIMI major bleeding and in-hospital major adverse events.[24] These results are also compatible with our findings. However, we found no time-dependent effectiveness in heparin administration. As previous literature has reported, antithrombotic activity of UFH immediately begins following the administration; nevertheless, it has been established that the enhancement in fibrinolysis activities of UFH 5000 IU initiates when tissue plasminogen activator (tPA) levels rise, which is almost 1 hour (60 minutes) after infusion, and it is prone to variability between and within individuals.[11]

Conclusion

Collectively, we found no difference in early or late heparin administration in STEMI patients' TIMI flow grade in this study. Our findings confirm that although effective, the heparin injection is not time-dependent. To entirely clarify such remarkable real-life findings, further clinical trials on this topic would be mandatory.

Limitations: Our study should be considered in the context of some limitations. A total of 12 patients did not come for follow-up and were unable to reach out. The infarct size was not studied by cardiac magnetic resonance imaging (cMRI) to further support the mortality results. However, as equal heparin was given irrespective of the STEMI severity, any probable differences as a result of survivor bias would be small. Additionally, information on the dual antiplatelet therapy administration at long-term follow-up was not available. As a final point, a randomized multicenter clinical trial with greater sample size is required to prospectively confirm these results.

Acknowledgments

The authors gratefully appreciate all of the subjects who participated in this study. In addition, we appreciate the assistance given by Professor Arsalan Salari. The present study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

This study was performed in line with the principles of the 2013 version of the Declaration of Helsinki guideline. Approval was obtained from the Ethics Committee of Guilan University of Medical Sciences with the code number of IR.GUMS.REC.1399.056, and was registered to the clinical trial registration system with IRCT registration number of IRCT20170925036401N2. Written informed consent for participation was obtained from all subjects.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

AFM and SMM conceived and designed the work that led to the submission. SC and AV acquired data and searched the literature. AFM, SC, and AV played an important role in interpreting the results. AFM, SC, AV, and SMM drafted the manuscript.

All the authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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