Original Article

Heparin Initiation Before and After Femoral Arterial Access in Primary Percutaneous Coronary Intervention: Side Effects and Angiographic Success Rates

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) with the addition of potent antithrombotic medications is the best therapy recommended for ST-elevation myocardial infarction (STEMI). The prehospital administration of heparin is commonly prescribed in the absence of conclusive data supporting its administration time. We aimed to study the side effects of heparin administration, especially hematoma formation at the arterial access site, between patients who received it before and after femoral arterial access in PCI.

Methods: This prospectively randomized clinical trial studied 128 patients who were diagnosed with STEMI and candidated for primary PCI at Rajaie Cardiovascular, Medical, and Research Center. Ninety-six patients who fulfilled the inclusion criteria were enrolled and randomly allocated to 2 groups according to a random table. The first group received heparin before the establishment of the femoral arterial access in the catheterization laboratory or in the ambulance (as soon as possible), while the second group received intravenous heparin after arterial access insertion for primary PCI. The systemic side effects of heparin and its angiographic appearances were compared between the 2 groups.

Results: The administration of unfractionated heparin before femoral arterial access in primary PCI had no more hematoma formation than did heparin injection after femoral arterial access (P=0.03). The study was unable to make any judgments regarding the angiographic thrombus burden before primary PCI according to the time of heparin injection because of the low volume of the patients; nonetheless, there was no significant difference between the 2 groups concerning thrombus burden.

Conclusions: Heparin therapy before femoral arterial access in primary PCI had no deleterious effect on hematoma formation. ***(Iranian Heart Journal 2018; 19(4): 18-25)***

KEYWORDS: Heparin, Complication, Angiography, Primary PCI, Thrombus burden

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Although unfractionated heparin (UFH) has never been evaluated in the management of ST-elevation myocardial infarction (STEMI) in a controlled trial compared with a placebo in primary percutaneous intervention (PCI), its use is a Class I recommendation according to the latest European guidelines.[1,7] UFH has been broadly recommended as the best anticoagulant in STEMI managed with primary PCI, and it has been the subject of numerous open-label studies.[2] What has yet to be fully elucidated, however, is the optimal time for UFH injection in relation to hematoma formation and its benefits depending on the time of injection.[2]

Enoxaparin and bivalirudin have been tested in comparison with UFH in many studies, with large meta-analyses having suggested the superiority of enoxaparin over UFH for ischemic and hemorrhagic end points and mortality.[3,4] Previous research has also demonstrated that bivalirudin can reduce the rate of major bleeding due to acute stent thrombosis.[5]

Discovered in 1916, heparin acts via antithrombin, which is a plasma cofactor.[6] Heparin is a sulfated polysaccharide with a molecular weight of between 3000 and 30 000 Da (mean=15 000 Da). The major anticoagulant effect of heparin is produced by its inactivation of thrombin and activation of factor X (factor Xa) through an antithrombin-dependent mechanism. Heparin attaches to an antithrombin via a high-affinity pentasaccharide, which is present on about a third of heparin molecules. For the inhibition of thrombin, heparin must bind to both the coagulation enzyme and the antithrombin, whereas binding to the enzyme is not required for the inhibition of factor Xa.[6] Therefore, anticoagulants such UFH are the mainstay of primary PCI, and anticoagulants and anti-platelet agents are recommended in primary PCI.[7] Nonetheless, the optimal agents and the best time of administration are still under debate. Heparin is commonly used during PCI. The advantages of heparin over other anticoagulants include its high availability, familiarity among medical personnel, immediate onset of effects, low cost, rapid reversal of effects when necessary, and possible monitoring by lab tests.[7] It also has some disadvantages such as the risk of heparin-induced thrombocytopenia and variability in effectiveness.

In a prospective registry, there were no significant differences in the rates of in-hospital major adverse cardiac events or major bleeding after the prehospital initiation of UFH, enoxaparin, or bivalirudin in patients treated with primary PCI for STEMI.[8]

Despite the dearth of available clinical randomized trials, the prehospital administration of heparin has been common in practice for many a year now. Several studies have shown the effects of heparin pretreatment on the initial TIMI flow, but whether this strategy can affect the intracoronary thrombus burden and morbidity and mortality has not been studied broadly.

TASTE was a multicenter registry randomized clinical trial evaluating routine thrombus aspiration in patients undergoing primary PCI. [9,10]

Another study drew upon the data from the TASTE study and assessed the effects of heparin treatment at prehospital time on thrombus burden and the TIMI flow prior to PCI in a close-observational study of patients with STEMI. The patient characteristics, procedural variables, and follow-up information of 33 different Swedish and Icelandic PCI centers were registered. Thrombus burden and the TIMI flow in angiography were defined and registered. The primary end points were the presence of visible intracoronary thrombi (G_2-G_5) and total occlusion (TIMI 0) before PCI. The secondary end points were the side effects of heparin such as any bleeding, stroke, or any neurological complication during a hospital length of stay of 30 days and all-cause mortality. The results revealed that the patients

pretreated with heparin had a minor thrombus burden and a higher TIMI flow than did the patients without heparin pretreatment. In addition, total vessel occlusion was less likely in the heparin-protected group than in the reference group. The major finding was that heparin pretreatment in the patients with STEMI was associated with a low risk of intracoronary thrombus and total occlusion before PCI. In that study, the median time from electrocardiography to primary PCI in the heparin pretreatment group was 4 minutes. [11]

In another study on primary PCI, the patients were divided into 2 groups: group 1 was comprised of patients who were administered heparin at the time of STEMI diagnosis and were candidated for primary PCI, and group 2 consisted of patients who received heparin after transfer to the catheterization laboratory for primary PCI. The TIMI flow of the infarct-related artery was compared between these 2 groups, and the results demonstrated that the initiation of heparin at the time of STEMI diagnosis was able to improve the outcome significantly.[12]

Although UFH has been used for many years, it has never been evaluated against a placebo in STEMI–bearing in mind that the use of an injectable anticoagulant in STEMI patients treated with primary PCI is a Class I recommendation according to the European guidelines.[1,6]

Large meta-analyses have suggested that enoxaparin is superior to heparin in primary PCI in STEMI in terms of ischemic and hemorrhagic end points.

In light of the previous research indicating that an early UFH administration in primary PCI on patients presenting with STEMI has higher infarct-related artery initial patency in a time-dependent manner and a better clinical outcome, we conducted the present study to shed further light on the optimal administration time for heparin in terms of optimum effects and fewer side effects.

METHODS

The study population consisted of 128 subjects (70.8% male) at a mean age of 58 years who underwent primary PCI at Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran, because of STEMI between October 2016 and August 2017. The entire study population was administered UFH and antiplatelets and managed according to the protocol of the center for STEMI management. Written informed consent for study participation was obtained from all the patients, and the study protocol was approved by the institutional ethics committee.

According to a randomization table, the study participants were randomly divided into 2 groups. The sample size was determined to be 45 patients in each group according to the following formula:

$$n = \frac{Z_{1-\frac{\alpha}{2}}\sqrt{2PQ} + Z_{1-\beta}\sqrt{P_1 Q_1 + P_2 Q_2}}{(P_1 - P_2)^2}$$

where $p = \frac{P_1 P_2}{2}$, Q=1-P, Q_1=1-P , and Q_2=1-P_2.

Group I received 5000 units of UFH after STEMI diagnosis as soon as possible and before femoral arterial access, while Group II received 5000 units of UFU after femoral arterial access. Coronary angiography and PCI were performed in accordance with the protocols of the center. All the patients underwent coronary angiography and PCI via the right femoral artery. After the completion of the angiography, the patients either received an additional dose of heparin or no additional dose depending on their management plan, weight, and thrombus burden. The arterial access was removed at least 6 hours after the completion of PCI with a partial thromboplastin time of below 45 seconds.

Table 1. Baseline characteristics of the patients by treatment group

	Group I	Croup II	Total	*P*
Patient No (%)	48 (50%)	48 (50%)	96	
Male	39 (81.3%)	29 (60.4%)	68 (70.8%)	0.2
History of coronary artery disease	10 (20.8%)	12 (25%)	22 (22.9%)	0.627
Diabetes mellitus	9 (18.8%)	13 (27.1)	22 (22.9%)	0.33
Hypertension	26 (54.2%)	33 (48.9%)	59 (51.6%)	0.610
Hyperlipoproteinemia	6 (12.5%)	12 (26.1%)	18 (19.1%)	0.094
Current smoking	17 (33.4%)	12 (25.0%)	29 (30.5%)	0.296
Family history of coronary artery disease	2 (4.2%)	6(12.8%)	8 (8.4%)	0.131
Mean age	58.4	58.79		

Table 2. Paraclinical characteristics of the patients

	Group I	Croup II	Total	*P*
ECG Change				1.0
Precordial	26 (54.2%)	26 (54.2%)	52 (54.2%)	
Limb	22 (45.8%)	22 (45.8%)	44 (45.8%)	
Target Vessel				0.704
Left anterior descending	23 (47.9%)	19 (39.6%)	42 (43.8%)	
Left circumflex artery	3 (6.3%)	6 (12.5%)	9 (9.4%)	
Right coronary artery	19 (39.9%)	20 (41.7%)	39 (40.6%)	
Obtuse marginal	3 (6.3%)	3 (6.3%)	6 (6.3%)	
Left Ventricular Ejection Fraction	36.88%	34.94%		0.373

Table 3. Angiographic characteristics of the patients

	Group I	Croup II	Total	*P*
PCI				
No	5 (10.4%)	3 (6.3%)	8 (8.3%)	
PCI+stenting	41 (85.4%)	44 (91.7%)	85 (88.5%)	0.65
POBA	1 (2.1%)	0 (0%)	1 (1.0%)	
CABG	1 (2.1%)	1 (2.1%)	2 (2.1%)	
Stent Size	26.7708	27.4167		0.921
Thrombus Burden				
Grade 0	2 (4.3%)	3 (6.3%)	5 (5.3%)	
Grade I	5 (10.6%)	6 (12.5%)	11 (11.6%)	
Grade II	9 (19.1%)	8 (16.7%)	17 (17.9%)	0.584
Grade III	9 (19.1%)	9 (18.8%)	18 (18.9%)	
Grade IV	3 (6.4%)	4 (8.3%)	7 (7.4%)	

PCI, Percutaneous coronary intervention; POBA, Plain old balloon angioplasty; CABG, Coronary artery bypass grafting

Table 4. Access site complications

	Group I	Croup II	Total	*P*
Hematoma				
No	39 (81.3%)	41 (85.4%)	80 (83.3%)	0.30
Yes	9 (18.8%)	7 (14.6%)	16 (16.7%)	
Hematoma (PCI done)				
Grade 0	71 (88.8%)			
Hematoma				
Grade 0	39 (81.3%)	41 (85.4%)	80 (83.3%)	
Mild	7 (14.6%)	4 (8.3%)	11 (11.5%)	0.639
Moderate	2 (4.2%)	3 (6.3%)	5 (5.2%)	

PCI, Percutaneous coronary intervention

The clinical variables that were recorded and evaluated were comprised of age, sex, a history of coronary artery disease (CAD), the risk factors for CAD, leads of ST-elevation, the involved coronary artery territory, PCI done, PCI not done, the artery subjected to PCI, the thrombus burden of the involved artery, the left ventricular ejection fraction in echocardiography before PCI, hematoma formation 24 hours after PCI, the systemic side effects of UFH in angiography, and the total size of the stent.

The angiograms were evaluated by a single cardiologist, who graded thrombus burden and hematoma formation at the femoral arterial access site after 24 hours and the procedural success rate after 24 hours.

The main aim of this study was to compare the formation of hematoma and ecchymosis between the groups that received UFH before and after femoral arterial access.

Also compared between the 2 study groups were variables such as thrombus burden, the left ventricular ejection fraction in echocardiography, the length of the stents deployed, the appearance of no reflow after PCI, gastrointestinal bleeding, genitourinary bleeding, pseudoaneurysm formation, retroperitoneal hematoma formation, arteriovenous fistula formation, and the angiographic success rate of PCI.

The inclusion criteria were candidacy for primary PCI due to STEMI at Rajaie Cardiovascular, Medical, and Research Center and signing a written informed consent form for participation in the study. The exclusion criteria were comprised of being referred as accelerated or facilitated PCI, having any contraindication for anticoagulants or antiplatelet drugs, receiving any anticoagulant before STEMI, having an unstable condition before or until 24 hours after primary PCI and undergoing mechanical ventilation, and death 24 hours after primary PCI. Before entering the study, all the patients were provided with a brief explanation regarding the benefits and hazards of each strategy.

About 24 hours after selective coronary angiography, all the patients were clinically evaluated by a single cardiologist for the formation of hematoma and ecchymosis. Additionally, the systemic side effects of UFH–including gastrointestinal hemorrhage, genitourinary bleeding, and thrombocytopenia–were assessed via laboratory tests.

The 2 groups were compared in terms of thrombus burden in angiography, the final result of PCI, the TIMI flow, and the size of the stents deployed. The formation of hematoma and ecchymosis was categorized as Grade 0: no hematoma and ecchymosis; Grade I: scant hematoma and ecchymosis; Grade II: a hematoma diameter of more than 2 cm and less than 10 cm; and Grade III: a hematoma diameter of more than 10 cm. The angiographic thrombus burden was categorized as Grade 0: no thrombus; Grade I: possible thrombus; Grade II: small (greatest diameter $\leq$ ½ vessel diameter); Grade III: moderate (>½ but <2 times of the vessel diameter); Grade IV: larger than twice the size of the vessel diameter; and Grade V: impossible to grade because of total occlusion.

The TIMI flow was graded after the completion of PCI as 0, 1, 2, and 3 in accordance with the current standards.

RESULTS

The study population was comprised of 96 patients. There was no history of CAD in 77.1% of the patients, while it was reported in 22.9%; there was no significant difference between the 2 groups in this regard (*P*=0.627). Only 8.4% of the patients had a family history of CAD. Diabetes mellitus was reported in 22.9% of the subjects, but there was no significant difference with regard to this disease between the groups (*P*=0.331). Hypertension was found in 51.6% of the study population; the groups were not statistically significantly

different in this regard (*P*=0.61). A history of dyslipidemia was reported in 19.1% of the study subjects, with the difference between the study groups not constituting statistical significance (*P*=0.094). Cigarette smokers comprised 30.5% of the study population.

ST-elevation changes were observed in 54.2% of the study participants in the precordial leads and in 45.8% of the study patients in the limb leads, and there was no difference as regards the limb electrocardiographic changes between the 2 groups (*P*=1.0).

The target vessel was the left anterior descending coronary artery in 43.8% of the patients, the right coronary artery in 40.6%, the left circumflex artery in 9.4%, and the obtuse marginal in 6.3%.

No diagonal PCI was done in this study. The *P* value was 1.407 for this parameter between the 2 groups. PCI and stenting was performed on 88.5% of the patients and plain old balloon angioplasty on 1%. PCI was deemed unsuitable in 2.1% of the patients, who subsequently underwent coronary artery bypass grafting. Selective coronary angiography demonstrated that 8.3% of the patients had normal epicardial coronary arteries or mild CAD; however, there were no differences between the 2 groups for PCI and stenting, plain old balloon angioplasty, and medical follow-up (*P*=1.606). Selective coronary angiography also revealed thrombi in 5.3% of the patients. There were no statistically significant differences between the 2 study groups with respect to Grade I (G1) thrombus burden (11.6% of the patients), G2 thrombus burden (17.9%), G3 thrombus burden (18.9%), G4 thrombus burden (7.4%), and G5 thrombus burden (38.9%). The number of the patients in each thrombus burden group was small, and overall there was no difference between the 2 groups (*P*=0.755).

There was no hematoma or ecchymosis in 83.3% of the study population, while 16.7% of the subjects had hematoma the day after the angiography; the difference between the 2 groups in this regard was not statistically significant (*P*=0.584). Mild hematoma was reported in 14.6% of Group I and 8.3% of Group II, and moderate hematoma was reported in 4.2% of Group I and 6.3% of Group II; the differences between the groups failed to reach statistical significance. There was no significant hematoma in either group. Overall, there was no significant difference vis-à-vis the grade of hematoma between Group I and Group II (*P*=0.584).

The left ventricular ejection fraction determined via echocardiography prior to selective coronary angiography was 36.88% in Group I and 38.94% in Group II, without any statistically significant difference between the study groups (*P*=0.584).

The size of the stent was calculated as the exact size when only 1 stent was deployed. When 2 stents were deployed, the size of the stent was calculated as the sum of the length of the 2 stents minus 2 mm for overlap. The mean stent size was 26.7708 mm in Group I and 27.4167 mm in Group II, without any significant difference between the 2 groups (*P*=0.586). The stent size was, therefore, considered an incoherent parameter given the large differences in the sizes of the stents.

DISCUSSION

This prospective randomized clinical trial studied patients with STEMI who were managed in accordance with the standard protocol for primary PCI—including prehospital evaluation and diagnosis, the early initiation of dual antiplatelet drugs, and the establishment of right femoral access for selective coronary angiography and PCI.

We found no significant differences between the groups that received UFH before and after femoral arterial access in terms of the formation of hematoma and ecchymosis, retroperitoneal bleeding, and other systemic side effects. Although UFH had no significant systemic side effects in the 2 groups, our small sample volume precludes any generalizable conclusions in this regard.

Our results indicated that hematoma formation after PCI can be lessened significantly in an experienced high-volume center.

We conducted the present study based on the hypothesis that there may be differences between patients receiving UFH before femoral arterial access and those receiving UFH afterward with respect to the left ventricular ejection fraction, the size of the stent, and the burden of thrombi because of the time of the effect of heparin; nonetheless, we found no statistically significant differences between our 2 groups, which may have been in consequence of our small sample size. Future studies on larger populations can shed more light on this issue.

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