Original Article

Safety of enoxaparin versus unfractioned heparin in patients undergoing percutaneous coronary intervention using drug eluting stents: A pilot study

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Background: Unfractioned heparin (UFH) is the standard antithrombotic agent in elective percutaneous coronary intervention (PCI), but has its own limitations. Several studies have suggested intravenous enoxaparin as a safe and effective alternative but most of them are uncontrolled. Our main goal was to evaluate the safety of enoxaparin over UFH in PCI patients undergoing coronary stenting by drug eluting stents (DES).
Methods: We randomly assigned 195 patients undergoing PCI using DES to receive either 0.75 mg enoxaparin per kilogram of body weight or 10000 IU unfractioned heparin. The primary end point was the incidence of major or minor bleeding . The secondary end point was the incidence of acute coronary events (ST-elevation myocardial infarction, non ST-elevation myocardial infarction,and unstable angina) in the first 24 hours after PCI.
Results: The rate of major and minor bleedings was similar in the first 24 hours after procedure between enoxaparin group and UFH group (P value>0.05). The incidence of acute coronary events and mortality was also similar between two arms.
Conclusion: In DES based PCI , a single intravenous bolus of 0.75 mg of enoxaparin per kilogram is associated with similar rate of bleeding as compaired with UFH. Also the rates of ischemic events are not different for enoxaparin and UFH however larger trials are needed for definit conclusion.

Key words: Unfractioned heparin, Enoxaparin, PCI, DES.

Introduction

Guidelines from the American College of Cardiology, American Heart Association, and the European Society of Cardiology all recommend the use of intravenous unfractioned heparin (UFH) during percutaneous coronary intervention (PCI)[1, 2]. However, some restrictions of UFH, including the need for monitoring of coagulation, the narrow therapeutic dosage, the potential stimulation of platelet activation, and the risk of thrombocytopenia are indicative of the need for a better and safer anticoagulation regimens in this setting[3].

As an alternative option, the administration of low-molecular-weight heparin (LMWH) is increasing in patients with acute coronary syndrome (ACS) who undergo PCI[4-6], and in those undergoing elective procedures[7, 8].

LMWH produces a more predictable and stable dose response comparing to UFH (obviating the necessity for coagulation monitoring)

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and is considered to have a longer half-life as well as a greater ratio of anti-factor Xa activity to anti-factor IIa activity, which reduces the generation and activation of thrombin[3, 9]. Moreover, LMWH has less tendency to induce platelet activation, release of the von Willebrand factor, and inflammation[10-13].

Although there are good evidence for the therapeutic benefits of LMWH over UFH in the medical management of patients with a high-risk ACS[14-17], data regarding the use of LMWH in patients undergoing PCI are restricted, most studies are uncontrolled or limited by sample size[18-25].Also there is no study addressing specifically the safety of LMWH in DES based PCI. We conducted a randomized, controlled trial to evaluate the efficacy and safety of intravenous enoxaparin versus UFH in patients with coronary artery disease (CAD) who underwent PCI by DES.

Materials and Methods:

This was a prospective interventional study in patients with CAD referred for coronary angioplasty. Patients with atherosclerotic coronary artery disease (chronic stable angina or acute coronary syndromes) were included if they were candidate for PCI as a result of anginal pain unresponsive to the optimal dose of antianginal medications or intolerable adverse drug reactions in which it was impossible to continue medical treatment. Patients with clinical heart failure and ischemic involvement of a relatively large segments of myocardium were also entered the study. Exclusion criteria included patients aged 75 or older (because of the increased risk of bleeding with enoxaparin in this age group) , renal failure defined as creatinine clearance of 30 ml/min and / or creatinine≥2.5 mg/dl in male and creatinine≥2.0 mg/dl in female participants, and use of bare-metal stents. Patients with primary PCI were also excluded. Other exclusion criteria included patients receiving heparin or LMWH before randomization, unacceptable prothrombin time (PT) or platelet count, and patients with abnormal platelet function disorders or coagulopathies. The study was conducted according to declaration of Helsinki and local regulations. All patients were given written informed consents.

Eligible 195 patients were randomly assigned to receive an intravenous bolus of 10000 IU unfractionated heparin, or intravenous enoxaparin at a dose of 0.75 mg per kilogram during the procedure. All patients also took oral aspirin 325 mg/day and clopidogrel 450 mg before the procedure. Patients recommended remaining on clopidigrel for at least 3 months. Aspirin was suggested to be continued indefinitely. PCI procedures were performed according to standard techniques by two individual interventional cardiologists. Femoral vascular access sheaths were removed 3 hours after procedure in the unfractionated heparin group, and 20 minutes after the end of the PCI in the group of enoxaparin . In all patients hemoglobin was checked prior to and 4 hours following PCI procedure.

Patients were monitored for 24 hours after procedure at post-angiography ward. Electerocardiograms (ECGs) were obtained routinely immediately after and on discharge from all patients. ECGs were also ordered as clinically indicated in patients with anginal chest pain and / or dyspnea in association with cardiac

serum biomarkers including CK-MB and troponin I. Cardiac biomarkers were assessed at the onset of symptoms and 6 to 9 hours later.

The primary end point of the trial was the occurrence of bleeding during the first 24 hours following the index PCI, defined as hematoma at the femoral access site, uncontrolled bleeding or re-bleeding from access site despite manual local pressure for 30 minutes, pseudoaneurysm of femoral artery at the site of femoral sheath insertion, arterio-venous fistula formation at femoral sheath site, retroperitoneal hemorrhage, intracranial bleeding, gross hematuria not related to trauma, gastrointestinal hemorrhage, and epistaxis. Major bleeding was defined as clinically overt bleeding causing a decrease in hemoglobin ≥ 3 g/dl requiring transfusion of packed red cells or whole blood, bleedings which require surgical intervention to stop bleeding at the femoral sheath insertion site, intracranial bleeding, and retroperitoneal bleeding.

We also studied the incidence of acute coronary events within 24 hours after PCI including anginal chest pain with or without ECG ST-T changes, ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI), urgent revascularization (PCI or CABG), and mortality.

Statistical analysis:

Statistical analyses were performed with the SPSS software version 11.5 statistical package. Continuous variables were expressed as

Table1. Baseline characteristics of the study population

Characteristics	*Unfractioned Heparin (n=121)*	*LMWH (Enoxoparin) (n=74)*	*P Value*
Age (year)	58.0±7.23	55.0±5.95	0.003
Male gender	55.4	58.1	0.712
Hypertension	67.7	55.4	0.083
Hyperlipidemia	27.2	35.0	0.246
Diabetes mellitus	15.7	31.0	0.011
Cigarette smoking	25.6	40.5	0.055
History of CAD	15.7	10.8	0.337
Opium addict	9.0	14.8	0.216
Prior MI	62.8	51.3	0.115
Prior CVA	9.0	5.4	0.103
Previous PCI	13.2	10.8	0.163
Previous CABG	9.0	12.1	0.192
STEMI	10.7	17.5	0.174
NSTEMI	13.3	20.3	0.192
Unstable angina	76.0	62.2	0.039
LVEF<30%	3.5	5.4	0.523
Multivessel stenting	37.7	24.3	0.273
Stent length>13mm	43.0	36.5	0.439

Data are presented as mean ± SD or percentage

mean ± SD and categorical data as percentage. Statistical analyses were completed on the categorical variables using a chi-square or Fisher's exact test as required. Comparisons of continuous variables between the two groups were performed with t-tests. A p-value of <0.05 was judged significant.

Results:

Characteristics of the patients:

Baseline characteristics in both groups are presented in Table 1. The mean age of patients who received unfractioned heparin and enoxaparin was 58.0±7.2 and 55.0±5.9, respectively (P=0.003). There were no significant differences in characteristics between patients receiving heparin or those receiving enoxaparin other than there being more diabetics in the enoxaparin group and less patients presenting with unstable angina in the enoxaparin group.

Primary end point:

Femoral access site bleeding during the first 24 hours occurred in 4.9% of patients assigned to take UFH and 2.7% of patients assigned to take enoxoparin (Table 2). Transfusion rates during the first 24 hours after PCI were low (Table 2).

Table1. Complications and clinical events in the study population within 24 hour

Criteria	*Unfractioned Heparin (n=121)*	*LMWH (Enoxoparin) (n=74)*	*P Value*
Femoral sheet hematoma<6 cm	9.0	4.0	0.186
Femoral sheet hematoma >6 cm	0.0	0.0	-
Femoral sheet site bleeding	4.9	2.7	0.356
Decrease in hemoglobin<3 g/dl	18.8	14.8	0.549
Decrease in hemoglobin>3 g/dl	0.0	2.7	0.240
Blood transfusion required	1.6	4.0	0.281
Arterio-venous fistula	0.0	0.8	0.500
Pseudoaneurysm	0.0	0.8	0.500
Retroperitoneal bleeding	0.0	0.0	-
Gasterointestinal bleeding	0.0	0.0	-
Epistaxis	2.5	4.0	0.240
Cerebro-vascular accident	0.0	0.0	-
Atypical chest pain	6.6	13.5	0.106
Medically controlled chest pain	4.1	4.1	0.999
Medically uncontrolled chest pain	6.6	6.8	0.969
Anginal chest pain with EKG changes	4.9	4.0	0.534
ST-segment elevation ≥ 1 mm	1.6	1.3	0.186
ST-segment depression ≤ 1 mm	1.5	0.0	0.293
T-inversion ≥ 2 mm	0.8	2.7	0.083
Cardiac biomarkers rising	4.1	4.0	0.643
Emergent angiography	12.3	8.1	0.349
Repeated PCI	1.6	1.3	0.678
Emergency CABG	1.6	1.3	0.678

Data are presented as mean ± SD or percentage

An insignificant drop in hemoglobin was observed in 22(18.8%) of patients receiving heparin and 11(14.8%) of patients on enoxaparin (P=0.549). Hemoglobin drop ≥ 3g/dl was found in only two patients whom both were in enoxaparin group. The cause of severe hemoglobin drop was arterio-venous fistula in one patient and pseudoaneurysm in the other one. Both patients required surgical repair at the sheath site and also blood transfusion. Hematomas at the sheath site occurred in 9.0% of patients receiving UFH compared to 4.0% on enoxaparin (P=0.186).

Secondary end points:

At the study period, there were no deaths. As shown in Table 2, there were no significant differences in end points variables in patients who received UFH or those who took enoxaparin. Regarding patients with anginal chest pain without ST-T ECG changes within the first 24 hours following PCI, of a total 39 patients, 21patints (53.8%) were in UFH and 18 patients (46.2%) were in enoxaparin group; the difference was not statistically significant. Anginal chest pain with ST-T ECG changes within the first 24 hours after PCI was seen in 9 patients (4.6%); 6 patients (66.7%) were in UFH and 3 patients (33.3%) in enoxaparin group. Type of EKG changes for each group are listed in Table 2 which was not statistically different. In total six patients required urgent, unplanned revascularization during the study period. There were 2 patients receiving enoxaparin who required urgent CABG; one case had developed acute in-stent thrombosis and the second one complicated with coronary artery dissection. One case in UFH group also suffered from acute in-stent thrombosis that underwent urgent CABG consequently. No mortality occurred in either study groups.

Discussion

We tried to compare the safety and feasibility of enoxaparin versus conventional intravenous unfractioned heparin for elective PCI procedures in the era of drug-eluting stents, and almost universal usage of clopidogrel. We found that the safety and procedural outcome of PCI were very similar in the two groups. Particularly, the incidence of bleeding was not statistically different, despite the shorter indwelling sheath time in the enoxaparin group as compared to UFH group. With enoxaparin, the treatment protocol was simple, administered as a single intravenous dose of 0.75 mg per kilogram before starting the intervention procedure, without anticoagulation monitoring; and twenty minutes after PCI, removal of the sheath was done. Collet et al. were the first to revealed that PCI could safely be performed without additional anticoagulation and without need for coagulation monitoring. However, this study was limited by the lack of a control group[4].

The present investigation is in accordance with the evidence from large-scale Superior Yield of the New Strategy of Enoxaparin , Revascularization, and GP IIb/IIIa inhibitors (SYNERGY) study that demonstrated the safety of PCI performance in patients with acute coronary syndromes pretreated with enoxaparin, without an excess rate of abrupt closure, compared with control patients who received

UFH (1.3% vs. 1.7%, p=NS)[6]. The result of meta-analysis of 8 randomized trials by De Luca et al. also demonstrated that LMWHs are associated with a significant decrease in re-infarction, trend in benefits in deaths, but higher risk of major bleeding complications[26].

The Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin (CRUISE) study randomized 261 patients undergoing PCI to receive enoxaparin or heparin with concomitant double-bolus eptifibatide therapy[27]. This study revealed similar rates of bleeding complications, vascular access site complications, and ischemic events between the two study arms. The Assessment of Combination Therapy in Obstructed Native Coronary Arteries (ACTION) trial compared enoxaparin with heparin during elective PCI performed with adjunctive small-molecule GP IIb/IIIa blockade[25]. The study showed that 0.75 mg/kg of enoxaparin achieved therapeutic levels of anticoagulation during the procedure without an excess of bleeding or ischemic complications compared with heparin. The ACTION and CRUISE trials lend support to the strategy of using enoxaparin during elective PCI; however, these studies are limited by small sample size.

The recently completed The Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE) trial randomized 3528 patients who underwent elective PCI to receive enoxaparin (0.75 or 0.5 mg/kg intravenously) or heparin, thus permitting a definitive safety comparison of these 2 therapies[28]. The slightly but not significantly higher death rate with low-dose enoxaparin remains unexplained and the trial was not large enough to provide a definitive comparison of efficacy in the prevention of ischemic events.

Our study was a randomized trial that lacked statistical power to demonstrate significant differences in clinical end points between enoxaparin and heparin groups. However, enoxaparin seems to be at least as safe as UFH regarding bleeding complications in the setting of DES based PCI. Larger randomized control trials are required to better characterize the definitive efficacy and safety of enoxaparin over UFH during PCI.

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