Original Article

Randomized, Blinded Trial Comparing Enoxaparin with Unfractionated Heparin in Patients Undergoing Contemporary Percutaneous Coronary Intervention

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Abstract

Background: *This study was designed to examine a unique and low dose use of intravenous enoxaparin in elective percutaneous coronary intervention (PCI) that would be applicable to an unselected population regardless of age, weight, and renal function. There is limited experience in anticoagulation using intravenous low-molecular-weight heparin in PCI.*

Methods: *A total of 100 consecutive patients undergoing elective PCI were treated with a single IV bolus of enoxaparin (0.5mg/kg) in group A of patients (n=50) or with unfractionated heparin in group B of patients (n=50). Sheaths were removed immediately after the procedure in patients treated with enoxaparin and some hours later in those treated with unfractionated heparin.*

Results: *In group A, ACT was 124.6±9.3 before PCI and 149.2±17.1 after that (P<0.05). In group B, one patient (2.9%) developed groin hematoma. No deaths, MI, or urgent target vessel revascularization were reported.*

Conclusion: *Low- dose (0.5 mg/kg) IV enoxaparin allows a target level of anticoagulation in patients undergoing PCI, appears to be safe and effective, allows immediate sheath removal, and does not require dose adjustment.*

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Introduction

Unfractionated heparin (UFH) has traditionally been used to prevent complications in patients undergoing percutaneous coronary intervention (PCI).[1,2] UFH exerts its anticoagulant effect by catalyzing the inhibition of thrombin and factor

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Xa by antithrombin. UHF has several important limitations, including its unpredictable anticoagulant effect necessitating careful laboratory monitoring, high protein binding, and inactivation by platelet factor 4.[3] To overcome some of these limitations, newer agents with more predictable anticoagulant effects and with greater anti-factor Xa activity are being evaluated. Factor Xa occupies a pivotal role in the clotting cascade because it is the final common pathway linking the intrinsic and extrinsic systems leading to the generation of thrombin.[3,4]

Low molecular weight heparins (LMWHs) are rapidly emerging as an alternation form of anticoagulant therapy to the standard unfractionated heparin (UFH). They are formed by controlled enzymatic or chemical deploymerization of UFH producing monosaccharide chains of varying lengths (3 to 7 kD) but with a mean molecular weight of ~5 kD.[5] Similar to UFH, LMWHs exert their anticoagulant activity by activating AT III. The principal difference between LMWHs and UFH lies in their relative abilities to catalyze the inactivation of factor-Xa and factor-IIa, which is dependent upon the relative composition of molecules with high affinity to AT III, called high-affinity molecules.[6] They exist in two functionally different forms; below critical length molecules (BCLM) (5-17 monosaccharide units<5.4 kD), which catalyze factor-Xa inactivation but not factor-IIa, and above critical length molecules (ACLM) (>18 monosaccharide units >5.4 kD), which catalyze the inactivation of both factor-Xa and thrombin and inhibit thrombin generation. UFH is mostly composed of ACLM, whereas less than half of the chains of LMWHs contain ACLM.[5]

LMWHs have greater activity against factor-Xa, are less bound to plasma proteins, endothelial cells and platelets, are resistant to inactivation by PF4, and are efficient inhibitors of thrombin generation.[6]

In addition, LMWHs also have a reduced potential to cause bleeding compared with UFH because they are less likely to increase microvascular permeability or interfere with platelet-vessel wall interaction.[6,7]

There are significant differences among LMWHs with respect to the ratio of anti-Xa to anti-IIa activity. An LMWH with the highest percentage of BCLM and the lowest percentage of ACLM is likely to exhibit superior pharmacologic efficacy. Currently, among LMWHs enoxaparin has the highest percentage of BCLM.[6,8] Enoxaparin has shown to provide the fastest peak of anti-Xa activity (3 to 4 h), the highest bioavailability, and the longest duration of anti-Xa activity (~ 12 h) after a subcutaneous injection compared with dalteparin and nadroparin.[9]

The key question whether these pharmacologic differences translate into differences in clinical outcomes remains largely unresolved. The logistic ease of administration without the need for monitoring anticoagulation appears to be the major advantage over UFH.[6]

Methods

Patient population

A total of 100 consecutive patients admitted for elective PCI were enrolled in the study. All the patients were>18 years old and were referred for elective PCI of a native vessel stenosis>60%. Exclusion criteria were primary PCI for ST-elevation MI, thrombolytic therapy for STEMI in the previous 24 hours (rescue PCI), LMWHs or UFH within the last 48 hours before PCI, or a GP IIb-IIIa antagonist within the previous two weeks. The study was approved by the Ethical Committee of the Cardiovascular Research Center, and informed consent was obtained from all the patients.

Study Medications

The patients were randomized to receive either enoxaparin in group A (0.5 mg/kg) or UFH in group B (100U/kg). Near-patient ACT monitoring was used for all the patients before and after the procedure. The patients received aspirin with a daily dose of 80 or 325mg. Clopidogrel (300mg) was administered immediately after coronary angiography except to patients who had previously received clopidogrel and then 75mg per day was administered. GP IIb-IIIa inhibitors were not used in this study. The use of any other medications was left to the discretion of the investigator in accordance with the ACC guidelines.

Procedures for PCI

PCI was performed later after a coronary angiogram using standard techniques, the femoral approach, and 6F or 7F guiding catheter in all the patients. Vascular access site sheaths were removed with manual compression immediately after PCI if enoxaparin was administered and were removed several hours later if PCI was performed with UFH when PTT measurement reached below 60 seconds. The patients were allowed to walk the next morning (bed-rest time>12 hours), and they left the hospital on the next day.

Clinical follow-up

In-hospital follow-up was based on physical examination, electrocardiogram (ECG), and CK and CK-MB levels. ECG and markers of periprocedural myonecrosis were determined systematically in all the patients before PCI and 6 to 8 hours and 12 to 14 hours after PCI.

All the patients in this study were followed up at one month by written questionnaires or telephone interviews. The information obtained was relative to living status, rehospitalization, reinfarction, subsequent cardiac catheterization or revascularization, and any form of

bleeding. The outcome end point was defined as a composite of death, myocardial infarction (MI), and urgent target vessel revascularization. Myocardial infarction was defined as recurrent chest pain and/or ECG changes with at least one of the following: Troponin-I positive, with levels of CK>2 times the upper limit of normal and an increase of >50% of the previous value, or the appearance of a new left bundle branch block or new Q waves. Urgent revascularization was defined as urgent PCI or coronary artery bypass grafting necessitated by the recurrent ischemia of the target vessel. Bleeding definition was adapted from the Thrombolysis In Myocardial Infarction (TIMI) criteria. Major hemorrhage corresponded to: 1) bleeding resulting in death or requiring surgery; 2) bleeding in an intracranial or intraocular location; and 3) a drop in the serum concentration of hemoglobin ≥5g/dl (or >15% of the hematocrit value). Minor bleeding was any clinically important bleeding that did not qualify as major or that was not clinically identified but associated with a drop in the serum hemoglobin concentration >4 g/dl or >12 % of the hematocrit level.

Statistical Analysis

Continuous variables are expressed as mean±SD, and dichotomous variables as frequencies. Categorical variables were compared using the chi-square test and continuous variables by using the Student's t-test. P values<0.05 were considered statistically significant.

Results

A total of 100 consecutive patients, who underwent elective PCI to treat 115 coronary lesions, were enrolled in this study. Table 1 shows the patients' baseline and angiographic characteristics.

Mean age was 55.94±8.1 years in group A (enoxaparin) and 55.51±9.3 in group B (UFH) (P<0.02). There was no significant difference between group A and B for coronary risk factors (P<0.05). Also, there was no significant difference between two groups for target vessel involvement. Multiple vessels angioplasty was performed in 15 patients (15%). A stent was implanted in 115 of the 115 de novo lesions (100%).

In group A, ACT was 124.6±9.3 before PCI and 149.2±17.1 after that (P>0.05).

In group B, one patient (2.9%) developed groin hematoma. This patient's ACT was 90 before PCI and 330 at the end of the procedure.

Vascular access site sheath was removed 6 hours later with an acceptable PTT (below 60 seconds).

Follow-up was obtained in all the patients. No deaths, MI, or urgent target vessel revascularization were reported.

Table 1. Baseline Clinical Characteristics of Enrolled Patients

Age (yr)*	55.65±7.8
Age>75 yrs, n (%)	6 (6%)
Men, n (%)	73 (73%)
Left ventricular ejection fraction*, %	55±8%
Risk factors, n (%)	
Smoking	30 (30%)
Hypercholesterolemia	59 (59%)
Hypertension	45 (45%)
Diabetes mellitus	32 (32%)
Previous MI (>1month)	33(33%)
Recent MI (<1 month)	8 (8%)
Previous coronary angioplasty	10 (10%)
Peripheral vascular disease	15 (15%)
Previous stroke	3 (3%)
Target vessel of PCI	
Left anterior descending	47 (40%)
Left circumflex	30 (27%)
Right	38 (33%)
Saphenous vein graft	0 (0%)
Left main	0 (0%)

*Mean±SD

Discussion

The purpose of this study was to assess the feasibility of using enoxaparin during PCI and to explore the risk (either bleeding or periprocedural clinical complication). We acknowledge that smaller differences between the groups are detectable given the modest sample size.

Our data suggest that a single IV bolus of 0.5 mg/kg enoxaparin is feasible in elective PCI. This reduced dose allows reaching the prespecified level of anticoagulation without dose adjustment or coagulation monitoring, which simplifies anticoagulation management during the procedure, allows immediate sheath removal when PCI is performed with enoxaparin alone, and provides similar anticoagulation and safety in patients, irrespective of advanced age, renal dysfunction, or being overweight.[10]

Unfractionated heparin has been the primary anticoagulant therapy for PCI for more than 20 years, but the optimal dose and the ideal target activated clotting time (ACT) remains uncertain and controversial.[6,11] The low bioavailability, unpredictable anticoagulant response, activation of platelets, unsatisfactory correlation between measurements of ACT and PTT, device-to-device variations in ACT measurements, and the lack of net prospective evaluations to correlate ACT measurements to clinical outcomes associated with UFH have led to empirical recommendations for both UFH doses and ACT target values.[11,12]

Although LMWH dose not have the same disadvantages as UFH, the ideal regimen for its use in PCI has yet to be determined. However, the predictable anticoagulant response

following a single IV dose of LMWH suggests that neither dose adjustment nor on-site coagulation monitoring is necessary.[13] The risk of overdose with a single IV dose is not related to the degree of subcutaneous resorption and should be much less dependent on renal function.[14]

The reduced dose of enoxaparin used here allowed safe immediate sheath withdrawal with manual compression favoring expeditive care for these elective cases.

Clearly, our study is not sized or designed to draw any definite conclusion on the use of this low dose of enoxaparin. Be that as it may, our study provides the first evaluation of a low dose of IV enoxaparin in nonselected patients in a research center in Iran. These data may aid the design of future randomized trials comparing LMWH with UFH in PCI.

Conclusion

Low- dose (0.5 mg/kg) IV enoxaparin allows a target level of anticoagulation in patients undergoing PCI, appears to be safe and effective, allows immediate sheath removal and does not require dose adjustment.

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