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Prospective, Randomized, Preliminary Clinical Trial with Low-Molecular-Weight Heparin or Unfractionated Heparin as Periprocedural Anticoagulant during Elective Percutaneous Coronary Intervention

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ABSTRACT

Background and Objectives : LMWH as a periprocedural anticoagulant during PCI has not yet been extensively studied. The aim of this study is to compare the clinical outcomes of enoxaparin to those of unfractionated heparin (UH) during elective PCI. **Subjects and Methods :** The eligible patients were randomized 1 : 1 into two treatment arms, either a single IV bolus of enoxaparin (75 IU/kg) or UH (100 IU/kg). The patients who had received any anticoagulants at therapeutic doses were excluded in this study. Data on patient characteristics, angiographic complications, laboratory variables and the in-hospital and 1-month clinical outcomes were compared between the two groups. **Results :** Of the 139 patients enrolled in this study, 68 received enoxaparin and 71 received UH. The patients' demographic and angiographic characteristics (gender, weight, creatinine and the PCI target vessel) were not different except for age between the groups. Multi-vessel angioplasty was performed in 59 (42.4%) patients. At least one stent was implanted in 130 (93.5%) patients. The sheath was removed immediately after PCI, except for one case, and then a collagen plug was applied in all the cases. There were no significant differences in angiographic complications like no reflow, thrombus at the treated lesion site, occlusion of collateral branches, distal embolism, dissection, coronary rupture or abrupt closure. Cardiac markers including CK (6 [8.8%] in the LMWH group vs 8 [11.3%] in the UH group), CK-MB (6 [8.8%] vs 8 [11.3%], respectively), and troponin-I (6 [8.8%] vs 10 [14.1%], respectively) were slightly increased after PCI compared to the last value obtained before the procedure in both groups, but the differences were not statistically significant. One patient in the enoxaparin arm and 2 patients in the UH arm developed NSTEMI during their admission. Four patients from the UH arm and 3 from the enoxaparin arm experienced hematoma at the puncture site. After discharge, no other events were reported at the 1-month follow-up. **Conclusion :** The use of enoxaparin (75 IU/kg) during elective PCI was effective and safe as using UH. Enoxaparin could be used like UH as a periprocedural anticoagulant in the elective PCI setting. **(Korean Circulation J 2006;36:573-577)**

KEY WORDS : Enoxaparin ; Anticoagulants.

Introduction

Unfractionated heparin has been widely used as one of the anticoagulants for percutaneous coronary intervention, although little data exists regarding the optimal extent of the activated partial thromboplastin time (aPTT) or regarding the activated clotting time (ACT) prolongation. It has been shown that ACT is inversely related to the likelihood of abrupt closure, but a minimum target value of ACT has not been identified.[1] High procedural ACTs are associated with an increased risk of bleeding.[2]

Enoxaparin has been shown to be equal or superior to unfractionated heparin (UH) for the patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI) and acute ST elevation myocar-

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dial infarction.[3-7] Recent studies have also shown good results with administering subcutaneous or intravenous enoxaparin to institute periprocedural anticoagulation for the patients with UA/NSTEMI.[8-10] However, Enoxaparin as periprocedural anticoagulation therapy during elective PCI has not yet been extensively studied, and the optimal anticoagulation in this setting still remains under debate.[11-13]

The aim of this study is to compare clinical outcomes of enoxaparin, which is one of the LMWHs, to those of unfractionated heparin (UH) during elective PCI.

Subjects and Methods

The study population consisted of consecutive patients of either sex who were >20 years old and who were admitted for elective percutaneous coronary intervention (PCI). All the patients had symptomatic stable angina, unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction for the previous 48 hours. Some of the patients were excluded if they had a platelet count <100,000/mm^3, acute myocardial infarction within the previous 48 hours, primary PCI, if they had been administered any anticoagulants at therapeutic doses when the catheterization was started and/or they didn't give us an informed consent.

Percutaneous 7Fr vascular sheaths were inserted by the modified Seldinger technique via femoral arterial access. Guiding angiograms were obtained with using ionic contrast.

The eligible patients were randomized 1 : 1 into two treatment arms, i.e., either a single IV bolus of enoxaparin (75 IU/kg) or UH (100 IU/kg). The Enoxaparin arm group did not receive a booster, but the unfractionated heparin arm group received additional boluses of 30 IU/kg per 1 hour. None of patients had their ACT or aPTT checked.

PCI was performed with using the standard techniques. Intracoronary nitroglycerin (200 ug) was administered before the lesion was crossed, and the dose was repeated when necessary. Procedural success was defined as a final diameter stenosis of ≤35% and no flow-limiting dissection. Intracoronary stents were recommended only for those patients with suboptimal angiographic results. The use of further anticoagulation after the procedure, including enoxaparin, unfractionated heparin or coumadin, was discouraged in all patients.

The sheath was removed immediately after PCI, except for one case, and then a collagen plug was applied in all cases.

End points

Blood samples for measuring the CK, CK-MB and Troponin-I values were obtained at pre-PCI, and at 6, 12, 18 and 24 h post-PCI. The hemoglobin levels and platelet counts were measured and an electrocardiogram was taken at baseline and 24 h after PCI.

Other safety parameters assessed included any major and minor bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) criteria,[14] the need for transfusion, thrombocytopenia (defined as a platelet count of <50,000/mm^3 or as a decrease of 50% from the previous platelet count), groin complications (a hematoma 5 cm in diameter or bleeding that required medical intervention, vascular repair or that led to prolonged hospitalization), and/or hemorrhagic stroke at 48 h post-PCI.

The efficacy end points were death, myocardial infarction (defined as creatine kinase level of >3× the upper limit of normal value after PCI and >50% of the previous value or new Q-waves in two or more contiguous leads), and urgent revascularization (PCI or coronary artery bypass grafting) at 48 h, discharge and 30 days post PCI. All the angiographic complications (no reflow, thrombus at the treated lesion site, occlusion of collateral branches, distal embolism, major dissection, coronary rupture and abrupt vessel closure) were noted.

Statistical analysis

Statistical analyses were performed using SPSS11 statistical analysis software. Unless otherwise noted, any tests of the hypothesis were two-sided and $p<5\%$ were considered statistically significant. Potential associations between the clinical and biologic parameters were tested by univariate procedures using the Student *t* or the chi-square test. The results are expressed as means±SDs.

Results

The baseline characteristics of the patients in the enoxaparin and unfractionated heparin arms are listed in Table 1. Of the 139 patients enrolled in this study, 68 received enoxaparin and 71 received UH. There were no significant differences in the baseline characteristics between the two randomized groups except for age (Table 1). Multi-vessel angioplasty was performed in 59 (42.4%) patients. At least one stent was implanted in 130 (93.5%) patients. The sheath was removed immediately after PCI, except for one case, and then a collagen plug was applied in all cases. There were also no significant differences of the procedure data (Table 2) and the angiographic complications like no reflow, thrombus at the treated lesion site, occlusion of collateral branches, distal embolism, dissection, coronary rupture or abrupt closure (Table 3). The cardiac markers, including CK (8.8% in LMWH group vs 11.3% in UH group), CK-MB (8.8% vs 11.3%, respectively), and troponin-I (8.8% vs 14.1%, respectively) were slightly increased after PCI compared to the last value before the procedures in both groups, but

the differences were not statistically significant (Fig. 1). 4 patients from the UH arm and 3 from the enoxaparin arm had hematoma at the puncture site, but there were no blood transfusions within 24 h in either arm of the study. One patient in the enoxaparin arm and 2 patients in the UH arm developed NSTEMI during admission, but there were no significant differences. After discharge, no events were reported at the 1-month follow-up phone call (Fig. 2).

Table 1. Baseline characteristics of the patients randomized to the enoxaparin versus the unfractionated heparin groups

		Heparin (n=71) n (%)	Enoxaparin (n=68) n (%)	p
Gender				
Male (n (%))		45 (63.4)	46 (67.6)	NS
Female (n (%))		26 (36.6)	22 (32.4)	
Age (years)	Mean±SD	64.4±9.0	61.2±8.8	0.0354
Height (cm)	Mean±SD	161.8±8.0	163.6±9.8	NS
Weight (kg)	Mean±SD	63.9±9.2	65.4±9.2	NS
Any cardiovascular risk		59 (83.1)	56 (82.4)	NS
Current smoker		17 (23.9)	25 (36.8)	
Hypercholesterolemia		3 (4.2)	0	
Diabetes		22 (31.0)	24 (35.3)	
Hypertension		42 (59.2)	35 (51.5)	
Any previous cardiovascular history		19 (26.8)	15 (22.1)	NS
Myocardial infarction		11 (15.5)	5 (7.4)	
Coronary artery bypass graft		0	0	
PCI		17 (23.9)	15 (22.1)	
Any clinical presentation				NS
Asymptomatic		0	0	
Stable angina		37 (52.1)	29 (42.7)	
Unstable angina		17 (23.9)	22 (32.4)	
Non-ST-elevation MI		6 (8.5)	7 (10.3)	
ST segment elevation MI (≤12)		0	1 (1.5)	
ST segment elevation MI (12-30)		5 (7.0)	7 (10.3)	
Other situation		7 (9.9)	3 (4.4)	
Any Peri-PCI use of other antithrombotics		71 (100.0)	68 (100.0)	NS
Aspirin		67 (94.4)	66 (97.1)	
Ticlopidin		4 (5.6)	7 (10.3)	
Clopidogrel		66 (93.0)	59 (86.8)	
Abciximab		0	0	
Eptifibatide		0	0	
Tirofiban		0	0	
Any other medications		70 (98.6)	67 (98.5)	NS
Beta blocker		52 (73.2)	45 (66.2)	
ACE inhibitor		38 (53.5)	34 (47.2)	
Angiotensin II receptor blocker		12 (16.9)	14 (20.6)	
Statin		51 (71.8)	39 (57.4)	
Nitrate		50 (70.4)	46 (67.7)	
Insulin		0	0	
Oral hypoglycaemic		10 (14.1)	11 (16.2)	
Antiarrhythmic		0	0	

NS: non significant, MI: myocardial infarction, PCI: percutaneous coronary intervention, ACE inhibitor: angiotensin converting enzyme inhibitor

Discussion

The administration of low dose intravenous enoxaparin during elective PCI has been previously studied,[12] but LMWH compared with unfractionaed heparin as a periprocedural anticoagulant during elective PCI has not yet been extensively studied, and the optimal anticoagulation procedure in this setting still remains under debate.

Table 2. Angiographic and procedure data

	Heparin (n=71) n (%)	Enoxaparin (n=68) n (%)	p
Vessel treated			
Left main coronary artery	0	2 (2.9)	NS
Left anterior descending	40 (56.3)	38 (55.9)	NS
Coronary artery			
Left circumflex artery	24 (33.8)	26 (38.2)	NS
Right coronary artery	34 (47.9)	30 (44.1)	NS
Internal mammary artery graft	0	0	
Saphenous graft	0	0	
Number of lesions	71	68	NS
1	40 (56.3)	40 (58.8)	
2	29 (40.9)	22 (32.4)	
3	2 (2.8)	6 (8.8)	
>3	0	0	
Number of stents	70	63	NS
1	38 (54.3)	34 (54.0)	
2	21 (30.0)	18 (28.6)	
3	9 (12.9)	11 (17.5)	
>3	2 (2.8)	0	
Total length (mm) of stents; mean	32.2	32.7	NS
Method of hemostasis	71	68	-
Collagen plug	71 (100.0)	68 (100.0)	
Sheath removal	71	68	NS
Immediately after the procedure	70 (98.6)	68 (100.0)	
Delayed time of sheath removal	1 (1.4)	0	

NS: non significant

Table 3. Angiographic complications

	Heparin (n=71) n (%)	Enoxaparin (n=68) n (%)	p
No reflow	0	0	
Thrombus at the treated lesion site	0	0	
Occlusion of collateral braches	2 (2.8)	3 (4.4)	
Distal embolism	0	0	NS
Dissection	2 (2.8)	1 (1.5)	
Coronary rupture	0	0	
Abrupt closure	0	0	
Other	0	0	

NS: non significant

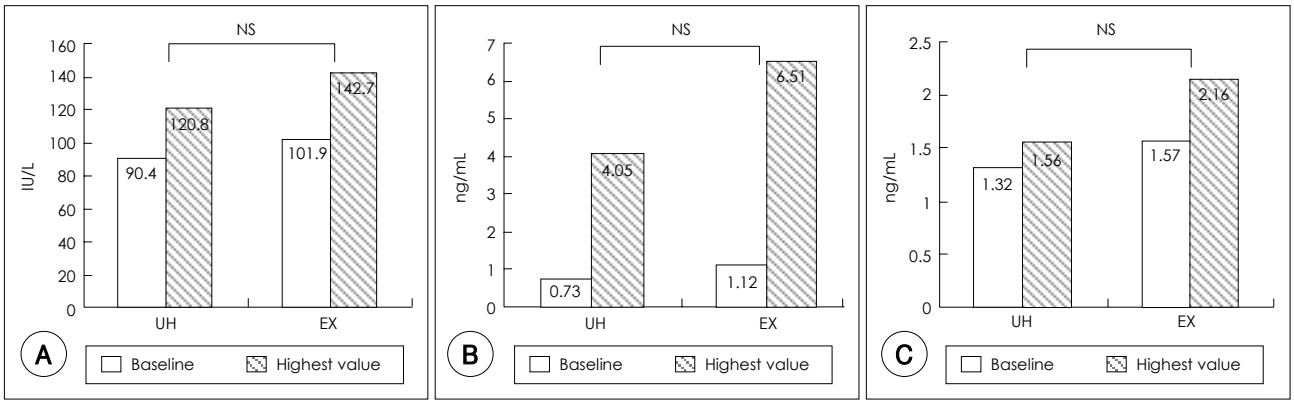

Fig. 1. Comparison of the cardiac markers: the cardiac markers were slightly increased after PCI compared to the baseline in both the UH group and the EX group, but the differences were not statistically significant in both groups. A: CK, B: CK-MB, C: troponin-I, UH: unfractioned heparin, EX: enoxaparin, NS: non-significant, PCI: percutaneous coronary intervention.

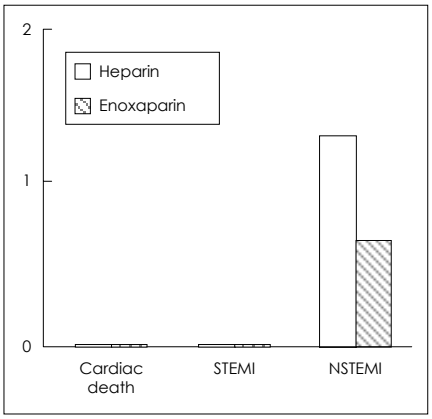

Fig. 2. Major cardiovascular event: 1 patient in the enoxaparin arm and 2 patients in the UH arm developed NSTEMI during admission, and then no other events were reported at 30 days follow-up. UH: unfractioned heparin, STEMI: ST segment elevated myocardial infarction, NSTEMI: non-ST segment elevated myocardial infarction.

Our data suggest that a single IV bolus of 75 IU/kg enoxaparin is feasible for elective PCI. This dosage allows the patient to reach the prespecified level of anticoagulation without dose adjustment or coagulation monitoring, which simplifies management of the anticoagulation during the procedure, and it allows immediate sheath removal when PCI is performed with a closure-device in both groups (the enoxaparin and unfractionated heparin groups).

Unfractionated heparin has been the primary anticoagulant therapy for PCI for a long time, but the optimal dose and the ideal target activated clotting time (ACT) remain uncertain and controversial.[15][16] The optimal anti-Xa target of enoxaparin in several studies (although these studies were somewhat limited) has been evaluated.[10][17] In some studies, a peak anti-Xa level for most patients was obtained from 0.5 IU/mL to 1.5 IU/mL because of safety considerations at a dosage of both 50 IU/kg intravenous and 100 IU/kg subcutaneous injections of enoxaparin; a peak anti-Xa >0.5 IU/mL was obtained in about 97.5% of patients.[8][12] The lack of a relationship between the occurrence of ischemic events or periprocedural MI and the periprocedural anti-Xa levels indicates the need for further evaluation of the dosage of enoxaparin.[9][12][18-22]

The National Investigators Collaborating on Enoxaparin (NICE)-1 registry established that a dose of 1 mg (100 IU)/kg of IV enoxaparin could be used during PCI, while the NICE-4 registry established the feasibility of administering 0.75 mg (75 IU)/kg of enoxaparin with abciximab in that setting.[9] In other study, a dose of 0.5 mg (50 IU)/kg of IV enoxaparin for elective PCI was also deemed effective and safe.[12]

Our data suggest that periprocedural anticoagulation using intravenous enoxaparin for elective PCI is effective in preventing the early angiographic complications of PCI and for ensuring a low event rate for bleeding complications and at the 1-month follow-up.

This study is limited by the low number of PCI patients. The anti-Xa activity was not checked and this was not used for the clinical decisions regarding PCI. The anti-Xa activity is known to be influenced by age, creatinine clearance and body weight, but in this study, there was a statistically different in the age of enoxaparin and unfractionated heparin groups. In addition, we could not decide an appropriate dosage of enoxaparin and we did not make comparisons with other closure devices or with not using a closure device after PCI. We used only short-term follow-up (1-month), and so we need long-term follow-up for the enoxaparin arm group.

Conclusions

In this report, an IV bolus of enoxaparin (75 IU/kg) during elective PCI appears to be equally effective and safe compared to UH. When considering the disadvantages of UH, including the low bioavailability, the unpredictable anticoagulant effect, activation of platelets and the necessity of monitoring the ACT or aPTT, enoxaparin could be used like UH as a periprocedural anticoagulant in the elective PCI setting.

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