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The use of Low Molecular Weight Heparin to Predict Clinical Outcome in Patients with Unstable Angina That Had Undergone Percutaneous Coronary Intervention

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Background : Antithrombotic therapy with heparin reduces the rate of ischemic events in patients with acute coronary syndrome. Low-molecular-weight heparin, given subcutaneously twice daily, has a more predictable anticoagulant effect than standard unfractionated heparin. Moreover, it is easier to administer and does not require monitoring.

Methods : We prospectively analyzed 180 patients with unstable angina who had undergone percutaneous coronary intervention (PCI) between 1999 and 2001 at Chonnam National University Hospital and had received either 120 U/kg of dalteparin (Fragmin®), administered subcutaneously twice daily (Group I; n=90, 61.8±8.9 years, male 67.8%), or had received continuous intravenous unfractionated heparin (Group II; n=90, 62.6±9.7 years, male 70.0%). During hospitalization and at 6 month after PCI, major adverse cardiac events such as acute myocardial infarction, target vessel revascularization, death, and restenosis were examined.

Results : During hospitalization, the incidence of acute myocardial infarction, target vessel revascularization and death were not different between the two groups. At follow-up coronary angiography 6 months after PCI, the incidence of restenosis was lower in group I than in group II (Group I; 26/90, 28.8% vs. Group II; 32/90, 35.6%, p=0.041) and the incidence of target vessel revascularization was lower in group I than in group II (Group I; 21/90, 23.3% vs. Group II; 27/90, 30.0%, p=0.039). No difference was found in the rates of major and minor hemorrhages, ischemic strokes or thrombocytopenia between two groups. By multivariate analysis, the factors related to restenosis were lesion length, postprocedural minimal luminal diameter, CRP on admission, diabetes mellitus, the type of heparin, and stent use.

Conclusion : Dalteparin, a low molecular weight heparin, is superior to standard unfractionated heparin in terms of reducing the restenosis rate and target vessel revascularization without increasing bleeding complications.

Key Words : Unstable angina; Percutaneous Coronary Intervention; Dalteparin; Unfractionated heparin

INTRODUCTION

In 1982, Telford and Wilson[1] introduced the idea of administering intravenous heparin for the treatment of the acute phase of unstable angina. This was followed by several important clinical trials, which evaluated the effect of heparin alone and in combination with aspirin[2-4]. The benefits of intravenous heparin as evidenced by such trials was judged to be sufficiently compelling to prompt authoritative bodies to recommend its use in the routine management of patients with unstable angina and acute myocardial infarction[5, 6].

However, a major limitation was unearthed in the Global

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Utilization of Streptokinase and tpA for Occluded Arteries (GUSTO I) study[7]. A marked clustering of reinfarctions was observed within hours after discontinuing unfractionated heparin (UFH) infusion. A plausible cause of these recurrent ischemic events after the cessation of heparin concerns the reactivation of the coagulation system. With the loss of therapeutic heparin levels, prothrombotic factors such as thrombin and tissue factor in the culprit lesion of the coronary artery could reactivate the coagulation system, rapidly resulting in thrombus growth and platelet recruitment with subsequent ischemia. So, the drugs that inhibit the coagulation pathway in the earlier phase, such as, low molecular weigh heparin (LWMH) may be more effective than UFH. Another limitation of UFH is that it may be difficult to maintain stable plasma levels of heparin, and frequent monitoring of activated partial thromboplastin time (aPTT) is needed[7].

Unlike UFH, LMWHs like dalteparin (Fragmin) are easy to administer subcutaneously twice daily, and may not require the monitoring of heparin plasma levels[8, 9]. In addition, LMWH has a higher anti-factor Xa/IIa ratio (2:1 vs. 1:1) and makes it easier to predict bioavailability[10, 11].

Many trials[12-14] have been undertaken to evaluate the effects of LMWH, and LMWH has been found to be more effective than UFH in terms of preventing death, acute myocardial infarction, and recurrent attacks of chest pain in patients with unstable angina/non-Q myocardial infarction, without increasing hemorrhagic complications.

We sought to observe the effects of LMWH in patients with unstable angina who had undergone percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

1. Subjects

All consecutive patients with unstable angina, who were admitted and underwent PCI and follow-up coronary angiography at the Heart Center of Chonnam National University Hospital between January 1999 and June 2001, were included in this study. All patients had a resting chest pain of more than 5 minutes' duration or a chest pain within 24 hours after admission. Patients with left bundle branch block, pacemaker insertion, ST segment elevation on resting electrocardiogram, or underlying heart disease, such as, congestive heart failure or arrhythmia, contraindications for anticoagulation therapy, or creatinine clearance of less than 30 mL/hour were excluded.

We used UFH and dalteparin alternatively in patients with unstable angina. One hundred and eighty patients were divided into two groups; Group I received dalteparin (n=90, 61.8±8.9 years-old, M:F=61:29) and Group II received UFH (n=90, 62.6±9.7 years-old, M:F=63:27). Clinical and angiographic characteristics, the success rate of PCI, and major adverse cardiac events were compared prospectively between the two groups during a six-month clinical follow-up.

2. Methods

Dalteparin was administered at 120 U per kilogram of body weight subcutaneously every 12 hours, and UFH as an intravenous bolus (usually 5000 units) followed by a continuous infusion at a dose adjusted according to the aPTT. Patients were treated with dalteparin or UFH for at least 48 h before PCI and 48 h after PCI. Dalteparin was administered for 5.2 days and UFH for 5.8 days.

3. Angiographic assessments

Left ventricular ejection fraction was compared by the Simpson method using two-dimensional echocardiography. A coronary angiogram was performed through the femoral or radial arteries. Coronary artery lesions were classified using the American College of Cardiology/American Heart Association system, in which a stenosis of more than 75% is defined as a significant lesion[15]. The lesion location, involved vessel number, lesion characteristics, and presence of an intracoronary thrombus on the coronary angiogram were compared between the two groups. Vessel patency of the infarct-related artery was assessed using the Thrombolysis in Myocardial Infarction (TIMI) flow score[16]. TIMI 0 was defined as a total occlusion without any distal flow below the lesion, TIMI 1 as trivial distal flow without complete visualization of the entire artery, TIMI 2 as complete visualization of the entire coronary artery with a slow flow rate and TIMI 3 as complete visualization of the entire artery with a normal flow rate. Successful revascularization was defined as a TIMI flow score of grade 3 with residual stenosis of less than 25%[16].

Complications of dalteparin or UFH were observed. Major hemorrhage was defined as bleeding resulting in death, as one requiring a transfusion of at least two units of blood, a fall in hemoglobin of 3 g/dL or more, or a retroperitoneal, intracranial, or intraocular hemorrhage. Minor hemorrhage was defined as any clinically important bleeding that did not qualify as a major hemorrhage, for example, epistaxis, ecchymosis or hematoma, or macroscopic hematuria[13]. 100~300 mg of aspirin was administered daily. UFH was administered to maintain an aPTT 2-fold higher than the normal controls. Patients were observed for major adverse cardiac events such as, acute myocardial infarction, target lesion revascularization, or death during hospitalization. After discharge from hospital, the patients were observed in the out-patient clinic at 4 week intervals, and the cardiovascular mortality was assessed

6 months after the PCI. A follow-up coronary angiogram was obtained for all patients at 6 months after PCI. The restenosis was defined as a diameter stenosis of more than 50%, by the Phillips quantitative coronary angiogram analysis system[17].

3. Statistical analysis

The unpaired *t*-test, Chi-square test and multiple logistic regression analysis were performed using SPSS-PC 10.0 (Statistical package for the social sciences, SPSS Inc. Chicago, IL, U.S.A.) and MS Windows®, and the results are presented as means±standard deviation. A *p* value of less than 0.05 was considered significant.

RESULTS

1. Clinical characteristics

Age and sex ratios did not differ between the two groups (*p*=0.637 and 0.788 respectively). No differences in risk factors such as hypertension, smoking, or hyperlipidemia were observed (*p*=0.543, 0.907, and 0.376, respectively) (Table 1). However, the incidence of diabetes mellitus was higher in group I (42.2%) than in group II (38.9%) (*p*=0.021) (Table 1). Past histories and ejection fraction and laboratory findings were no different (*p*=*NS*) (Table 1).

Table 1. Baseline clinical characteristics

	Dalteparin group (n=90)	UFH group (n=90)	*p* value
Age (yrs)	61.8± 8.9	62.6± 9.7	0.637
Male (%)	61 (67.8)	63 (70.0)	0.788
Diabetes mellitus (%)	38 (42.2)	27 (30.0)	0.021
Hypertension (%)	45 (50.0)	40 (44.4)	0.543
Smoking (%)	48 (53.3)	47 (52.2)	0.907
Dyslipidemia (%)	38 (42.2)	35 (38.9)	0.376
Prior MI (%)	2 (2.2)	1 (1.1)	0.547
Prior aspirin use (%)	14 (15.6)	16 (17.8)	0.850
Baseline EF (%)	59.6±13.0	58.3±12.3	0.342
CK-MB (mg/dL)	21.5±8.7	18.6±5.8	0.678
Troponin T (ng/mL)	1.8±1.6	1.5±1.3	0.290
Troponin I (ng/mL)	2.9±2.5	2.7±2.3	0.324
ESR (mg/dL)	15.4±8.8	23.4±11.3	0.449
CRP (mg/dL)	1.1±0.7	3.0±2.1	0.092

UFH, unfractionated heparin group; MI, myocardial infarction; EF, ejection fraction; ESR, erythrocyte sedimentation rate, CRP; C-reactive protein

2. Coronary angiographic characteristics

The number of vessels involved on diagnostic coronary angiography did not differ between the two groups (*p*=0.371) (Table 2). The order of frequency of the number of involved vessels was, single vessel disease, two- vessel disease and three-vessel disease.

Table 2. Coronary angiographic findings

	Dalteparin group (n=90)	UFH group (n=90)	*p* value
No. of involved vessel (%)			0.371
1 vessel	44 (48.9)	47 (52.2)	
2 vessel	28 (31.1)	29 (32.2)	
3 vessel	18 (20.0)	14 (15.6)	
Target coronary artery (%)			0.629
LAD	53 (58.9)	49 (54.4)	
LCX	25 (27.8)	27 (30.0)	
RCA	12 (13.3)	14 (15.6)	
TIMI flow (%)			0.485
0	6 (6.7)	5 (5.6)	
1	16 (17.8)	12 (13.3)	
2	21 (23.3)	25 (27.8)	
3	47 (52.2)	48 (53.3)	
mean TIMI flow	2.21±0.82	2.29±1.04	
ACC/AHA type (%)			0.583
Type A	4 (4.4)	0 (0.0)	
Type B_1	46 (51.2)	51 (56.7)	
Type B_2	20 (22.2)	15 (16.7)	
Type C	20 (22.2)	24 (26.6)	
Intracoronary thrombosis (%)	8 (8.9)	6 (6.7)	0.897
Intracoronary calcification (%)	5 (5.6)	6 (6.7)	0.932
Stent use (%)	68 (75.6)	63 (70.0)	0.312
Lesion length (%)			0.345
<20 mm	74 (82.2)	70 (77.8)	
≥20 mm	16 (17.8)	20 (22.2)	

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACC/AHA, American College of Cardiology/American Heart Association

Lesions involving the left anterior descending artery were the most common, but the lesion distribution did not differ between the two groups (*p*=0.629) (Table 2). Lesion morphology, assessed according to the ACC/AHA classification, was not significantly different between the two groups (*p*=0.583) (Table 2), and neither were intracoronary thrombus, intracoronary calcification or mean TIMI flow grade (*p*=0.897, 0.932 and 0.485, resp.) (Table 2).

The reference diameter, minimal luminal diameter and stenotic diameter were similar (*p*=0.508, 0.456, and 0.532, respectively) (Table 3). Follow-up coronary angiogram at 6 months after PCI indicated that the minimal luminal diameter of group I was higher than that of group II (1.81±0.49 vs. 1.64±0.44, *p*=0.035) (Table 3) and the diameter stenosis of group I was lower than that of group II (32.2±14.5% vs. 37.4 ±18.8%, *p*=0.041) (Table 3).

Table 3. Quantitative coronary angiographic results

	Dalteparin group (n=90)	UFH group (n=90)	*p* value
Reference diameter (mm)			
before PCI	2.98±0.58	2.95±0.67	0.508
after PCI	3.02±0.47	2.99±0.56	0.549
6-month follow-up	2.67±0.54	2.62±0.61	0.495
MLD (mm)			
before PCI	0.61±0.33	0.68±0.45	0.456
after PCI	2.70±0.46	2.65±0.51	0.498
6-month follow-up	1.81±0.49	1.64±0.44	0.035
Diameter stenosis (%)			
before PCI	79.5±12.6	76.9±15.7	0.532
after PCI	10.6±13.1	11.4±14.9	0.654
6-month follow-up	32.2±14.5	37.4±18.8	0.041

PCI, percutaneous coronary intervention; MLD, minimal luminal diameter

3. Major adverse cardiac events on admission and during 6 months of follow-up

During hospitalization, the two groups were similar in terms of the incidence of acute myocardial infarction, target lesion revascularization, and death (p=0.547, 0.578, and 0.544, respectively) (Table 4). However, at the 6 months follow-up, the occurrence of restenosis was significantly lower in group I (p=0.041), as was the number of cases with target lesion revascularization (p=0.039) (Table 4).

Table 4. Adverse clinical events

	Dalteparin group (n=90)	UFH group (n=90)	*p* value
In-hospital events (%)			
Acute myocardial infarction	1 (1.1)	2 (2.2)	0.547
Target vessel revascularization	3 (3.3)	4 (4.4)	0.578
Death	0 (0.0)	1 (1.1)	0.544
MACE	4 (4.4)	7 (7.7)	0.211
Follow-up events at 6 month (%)			
Restenosis	26 (28.8)	32 (35.6)	0.041
Target vessel revascularization	21 (23.3)	27 (30.0)	0.039
Death	2 (2.2)	5 (5.6)	0.278

MACE, major adverse cardiac events

4. Hemorrhagic and serious adverse events

The incidence of major hemorrhage, minor hemorrhage, ischemic stroke, thrombocytopenia in the two groups was similar (p=0.544, 0.488, 0.547 and 0.511, respectively) (Table 5).

Table 5. Hemorrhagic and serious adverse events

	Dalteparin group (n=90)	UFH group (n=90)	*p* value
Major hemorrhage (%)	0 (0.0)	1 (1.1)	0.544
Minor hemorrhage (%)	5 (5.6)	3 (3.3)	0.488
Ischemic stroke (%)	1 (1.1)	2 (2.2)	0.547
Thrombocytopenia < 100,000/mm^3	2 (2.2)	3 (3.3)	0.511

5. Multivariate analysis: Clinical and quantitative coronary angiographic predictors of coronary restenosis

Multiple logistic regression analysis was performed to identify independent predictors of coronary restenosis after PCI. Lesion length, post-PCI minimal luminal diameter, C-reactive protein on admission, diabetes mellitus, type of heparin, stent use were identified as independent predictor of restenosis after PCI, but the initial ejection fraction, hypertension, post-PCI TIMI flow, initial TIMI flow, number of involved vessels and target coronary artery were not (Table 6).

Table 6. Multivariate analysis: Clinical and quantitative coronary angiographic predictors of coronary restenosis

Variable	Odds ratio	95% CI	*p* value
Lesion length	8.89	2.04-25.06	0.001
Post-PCI MLD	7.53	2.46-20.61	0.001
CRP on admission	5.89	2.70-15.24	0.007
Diabetes mellitus	2.33	2.16- 4.54	0.011
Type of heparin	1.34	1.31- 3.39	0.022
Stent use	4.83	1.21-10.54	0.032
Initial ejection fraction	1.13	1.0 - 1.3	0.098
Hypertension	2.23	0.71- 9.84	0.325
Post-PCI TIMI flow	1.78	0.57- 7.32	0.342
Initial TIMI flow	1.64	0.77- 3.19	0.360
No. of involved vessel	1.32	0.61- 4.12	0.415
Target artery	1.42	0.42- 2.53	0.466

PCI, percutaneous coronary intervention; MLD, minimal luminal diameter; TIMI, Thrombolysis In Myocardial Infarction

DISCUSSION

Like UFH, LMWHs are glycosaminoglycans consisting of chains of alternating residues of D-glucosamine and uronic acid, either glucuronic or iduronic acids. UFH is a heterogeneous mixture of polysaccharide chains ranging in molecular weight from about 3000 to 30,000. LMWH contains fragments of UFH produced by controlled enzymatic or chemical depolymerization processes that produce chains with a mean

molecular weight of about 5,000[18, 19]. When compared to UFH, LMWH has a longer half-life, and it is easier to predict its bioavailability, and does not required is not needed the monitoring of heparin plasma levels[20].

LMWH has been used for the prevention and treatment of deep vein thrombosis[21, 22], but recently many trials have demonstrated that LMWH is very safe and effective anti-thrombotic drug for the prevention of arterial thrombotic disease[17, 23]. The Fragmin during Instability in Coronary Artery Disease (FRISC) study[24] evaluated combination antithrombotic therapy with aspirin and dalteparin versus aspirin alone in patients with acute coronary syndromes. A significant relative-risk reduction of 48 percent in the composite end point of death or myocardial infarction was identified during the first six days of treatment. Gurfinkel et al.[25] were the first to compare LMWH (nadroparin) and aspirin directly with standard intravenous UFH and aspirin and with aspirin alone. A decrease of more than 50 percent was observed in the rate of recurrent angina (44% vs. 21%) and a significant decrease in the rates of, silent ischemia, revascularization, and minor bleeding were observed in the group receiving LMWH as compared with the groups receiving heparin plus aspirin or aspirin alone. The Fragmin in Unstable Coronary Artery Disease (FRIC) study[26], a randomized but open-label (in the hospital phase) study involving 1500 patients with acute non-Q-wave coronary syndromes, compared LMWH (dalteparin) and aspirin with standard intravenous UFH and aspirin. The study, showed no difference in efficacy or in the incidence of hemorrhage between LMWH and UFH treated patients during the hospital phase. In contrast, the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study, found a significant reduction in the number of events during the first 14 days that this was sustained through to 30 days. Our study shows that the restenosis rate and the target lesion revascularization rate were lower in the dalteparin group than in the UFH group.

The incomplete and variable inhibition of thrombin by intravenous UFH stems in part from its relatively low bioavailability due to its extensive nonspecific binding to serum proteins, macrophages, and endothelial cells[27-29]. The catalytic activity of heparin preparations, which inhibit factor IIa and factor Xa resides in glycosaminoglycan chains, is dependent upon a pentasaccharide sequence for high-affinity binding to antithrombin[27]. High-affinity material is further subdivided into chains that are composed of more than 18 saccharide units, which are therefore, above the critical length mass (ACLM), needed to inhibit both factor IIa and factor Xa, and chains that are below the critical length mass (BCLM), and are therefore, able to inhibit only the early steps in the coagulation cascade and thrombin generation[27]. The BCLM:ACLM ratio of UFH is 1:1, whereas LMWH has ratios that are above 1, which leads to a higher anti-factor Xa:anti-factor IIa ratio. This provides a distinct kinetic advantage by inhibiting the early steps in the coagulation cascade and inhibiting thrombin generation. The maintenance of a sufficient concentration of anti-factor IIa activity in LMWH preparations is necessary to simultaneously inhibit thrombin activity. The greater bioavailability (91%) of LMWH produces a higher level of anti-factor IIa activity than UFH, thus potentially inhibiting thrombin activity to a greater extent[30]. The additional pharmacological advantages of LMWH versus UFH include a reduced sensitivity to the inhibitory effects of platelet factor 4, a greater capacity to release tissue-factor-pathway inhibitor, a lower propensity to promote the activation and aggregation of platelets, and it has potential antiplatelet effects by suppressing von Willebrand factor[31-36].

Cho et al.[37] evaluated 53 patients with intracoronary thrombus by coronary angiography. After dalteparin therapy, follow-up coronary angiograms showed TIMI grade 3 in 7 patients, TIMI grade 2 in 5 patients and TIMI grade 1 in 3 patients, and a decreased thrombosis index.

Major side effects of LMWH are hemorrhagic complication and thrombocytopenia. Cohen et al.[13] evaluated an UFH group and an enoxaparin group with respect to hemorrhagic complications. No difference was found in major hemorrhagic complications and thrombocytopenia, but the incidence of minor hemorrhage was higher in the enoxaparin group than in the UFH group (11.9% vs. 7.2%). Our study identified no differences in the incidences of major and minor hemorrhage or thrombocytopenia between the two groups.

In conclusion the present study shows that dalteparin, a low molecular weight heparin, is superior to standard unfractionated heparin in terms of reducing the restenosis rate and target vessel revascularization without increasing bleeding complications.

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