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Effects of unfractionated and low molecular weight heparins on plasma levels of hemostatic factors in patients with acute coronary syndromes

VIRTUDES VILA,* VICENTA MARTÍNEZ-SALES,* EDELMIRO RÉGANON,* ELISA PERIS,° FRANCISCA PEREZ,° MIGUEL RUANO,° JUSTO AZNAR#

*Research Center, °Coronary Care Unit, #Department of Clinical Pathology, La Fe University Hospital, Valencia, Spain

Correspondence: Virtudes Vila, M.D., Centro de Investigación, Hospital Universitario La Fe, Avda. Campanar, 21, 46009 Valencia, Spain. Phone: international +34-96-3862797. Fax: international +34-96-3868718. E-mail: reganon_ede@gva.es

Background and Objectives. Unfractionated heparin (UFH) and enoxaparin (low molecular weight heparin) constitute fundamental therapies in the treatment of patients with acute coronary syndrome (ACS). Since enoxaparin appears to offer clinical advantages over UFH in managing ACS, markers of thrombin generation, endothelial function and acute phase response could manifest different responses to UFH or enoxaparin. The purpose of the present study was to investigate the effect that treatment with either UFH or enoxaparin has on plasma hemostatic markers in 24 patients with ACS.

Design and Methods. The patients were randomized to receive 5,000 IU intravenous bolus and continuous infusion of 18 IU/Kg/h UFH (n=11) or 1 mg/kg/12h subcutaneous enoxaparin (n=13). The plasma levels of fibrinogen (Fg), prothrombin fragment 1+2 (F1+2), thrombin antithrombin complex (TAT), von Willebrand factor (vWF), tissue factor (TF) and tissue factor pathway inhibitor (TFPI) were assayed at admission and 6, 12, 24 and 48 hours after heparin treatment.

Results. Upon admission, UFH and enoxaparin patients showed a significant increase in all the hemostatic parameters measured with respect to the levels in the control subjects. In comparison with the baseline levels of the UFH- and enoxaparin-treated patients, Fg showed a significant increase at 48 h and TFPI at 6, 12 and 24 hours. However, at 48 hours TFPI levels were not significantly higher than the basal values. There were no significant changes in F1+2, TAT, vWF or TF.

Interpretation and Conclusions. Markers of thrombin generation, endothelial function and acute-phase reactants manifest a similar response to UFH and enoxaparin. An increase in thrombin generation may be a result of persistently activated inflammatory and endothelial processes, despite UFH and enoxaparin treatment.

Key words: unfractionated heparin, low molecular weight heparin, thrombin generation, endothelial function, acute coronary syndrome

The coagulation cascade becomes highly activated in unstable angina and non-Q-wave myocardial infarction, and this is reflected by an increase in markers of thrombin generation, such as prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin complex (TAT), and in those of fibrin formation such as fibrinopeptide A.[1-3] Elevated levels of von Willebrand factor (vWF) and fibrinogen (Fg) have been reported to be a risk factor for coronary heart disease.[4] Evidence that thrombin generation is involved in the thrombotic process provides a rationale for the use of heparin. Treatment with intravenous unfractionated heparin (UFH) in addition to aspirin effectively reduces the risk of death and myocardial infarction in the acute coronary syndrome (ACS).[5-8] Low molecular weight heparin (LMWH) has been rigorously evaluated as a tool for managing acute coronary ischemia. The results of clinical trials suggest that LMWH (enoxaparin, dalteparin and nadroparin) are effective and safe in the treatment of unstable angina and non-Q-wave myocardial infarction.[9] The results of large prospective randomized, comparative clinical trials, ESSENCE[10] and TIMI 11B,[11] have consistently demonstrated the superiority of enoxaparin over UFH in the management of ACS. Both LMWH and UFH exert their anticoagulant effect by accelerating the inhibitory action of antithrombin against its target proteases (i.e. factor Xa and thrombin),[12] and by mobilizing tissue factor pathway inhibitor (TFPI) from the vascular

endothelium into the blood circulation.[13] TFPI is a potent inhibitor of the initial step of the extrinsic coagulation system, which acts by neutralizing the catalytic activity of factor Xa and by feedback inhibition of the factor VIIa-tissue factor (TF) in the presence of factor Xa. Plasma TFPI is present in its free and lipoprotein-associated forms.[14] TFPI can be released in its free form from the endothelial surface into plasma by heparin[15] and exerts a much stronger anticoagulant effect than the lipoprotein-associated form.[16]

A previous study on unstable coronary syndromes comparing enoxaparin and UFH reported no significantly different effect on F1+2 and TAT after 72 hours of treatment.[17] However, there have been no reports about the comparative effects of enoxaparin and UFH on TF and TFPI plasma levels in ACS patients. On the other hand, the progression of acute-phase response and endothelial activity is concomitant with the increase in thrombin generation.[18] Since enoxaparin appears to offer clinical advantages over UFH in managing ACS,[10,11] the markers of thrombin generation, endothelial function and acute-phase reaction could manifest different responses to UFH and enoxaparin. Additional studies are therefore needed to define the relationship between these markers better and the effects of UFH and enoxaparin treatments on ACS.

The aim of our study was to evaluate the changes induced by UFH and enoxaparin in patients with unstable angina or non-Q-wave myocardial infarction during the first 48 hours of heparin treatment by measuring the plasma levels of hemostatic markers of thrombin generation, endothelial function and acute phase response (F1+2, TAT, TF, TFPI, vWF, Fg, HMW-Fg) and, in this way, obtain information that could explain the better clinical results observed with enoxaparin.

Design and Methods

Patients and study design

Twenty-four consecutive patients admitted to the Coronary Care Unit with acute coronary syndrome (ACS) without persistent ST-segment elevation were studied. Inclusion criteria were: 1) unstable angina, chest pain suggestive of ischemic origin lasting ≥5 minutes at rest within 24 hours before inclusion in the study and 2) non-Q-wave myocardial infarction, increase in serum cardiac markers (MB-CK>19 U/L). The major exclusion criteria were: previous anticoagulant therapy, hypertension (systolic blood pressure >180 or diastolic blood pressure >110 mmHg), a history of major surgery within the previous 1 month, history of central nervous system structural damage or other contraindications to anticoagulation, and patients who upon admission were considered candidates for immediate revascularization and received abciximab. At the time of hospital admission, all the patients received aspirin (200 mg/day). Subsequently, the patients were randomized to one of the following heparin treatments: 1) eleven patients received a 5,000 IU intravenous bolus followed by a continuous infusion of 18 IU/Kg/h UFH (Rovi, Spain); all these patients had an aPTT level higher than twice the baseline value from 6 to 48 hours; and 2) thirteen patients received 1 mg/kg/12h subcutaneous enoxaparin (Decipar, Italfarmaco S.A.). The control subjects consisted of thirty volunteers without significant stenosis of the coronary arteries, matched with the patient group for age and sex, who had taken no medication during the preceding two weeks.

All patients gave their informed consent to the protocol.

Blood sampling and processing

Specially trained nurses took blood samples from the patients by venipuncture before starting UFH and enoxaparin administration (baseline) and 6, 12, 24 and 48 h later. Blood was collected into Vacutainer tubes containing 0.129 M sodium citrate. The ratio of anticoagulant to blood was 1/9 (vol/vol). Each sample was immediately centrifuged at 3,000 g for 15 min at 4ºC and the plasmas were tested immediately or frozen in aliquots at –80ºC until used.

The plasma Fg concentration was measured by a heat precipitation assay,[19] which evaluates the protein concentration. The high molecular weight fibrinogen (HMW-Fg) level in plasma was identified and quantified by SDS-PAGE and immunoblotting.[20]

The following were determined by an ELISA method: plasma F1+2 level (Enzyngost F1+2 kit, Behring Diagnostics); plasma TAT level (Enzyngost TAT, Behring Diagnostics); plasma TF level (Immubind, Tissue factor ELISA kit, American Diagnostica); plasma total TFPI level (Asserachrom TFPI total, Diagnostica Stago); plasma vWF activity (Asserachrom vWF, Diagnostica Stago).

Statistical analysis

All the determinations were done at least in duplicate. All the data reported are expressed as mean ± standard deviation. Statistical comparisons between the two patient groups and healthy subjects were performed by use of one-way analysis of variance (ANOVA) followed by *post-hoc* analy-

Table 1. Baseline clinical characteristics of the patients.

	UFH (N=11)	*ENOX (N=13)*	*p*
Age (yr)	66±12	70±10	0.38
Sex (male)	6 (54)	8 (61)	0.73
AMI no-Q	7 (64)	5 (39)	0.22
Unstable angina	4 (36)	8 (61)	0.22
Diabetes	3 (27)	5 (38)	0.25
Hypercholesterolemia	4 (36)	7 (54)	0.58
Smoker	5 (45)	3 (23)	0.24
Hypertension	2 (18)	2 (15)	0.46

Data are presented as means ± standard deviation or number and percentages (in brackets) of patients treated with unfractionated heparin (UFH) and enoxaparin (ENOX).

sis with Bonferroni's correction for multiple comparisons. Statistical comparisons between patients' data at different times were performed using a paired-samples *t* test. All statistical calculations were performed on a statistical package (SPSS). A p value <0.05 was considered statistically significant.

Results

Twenty-four patients with unstable angina or non-Q-wave myocardial infarction who were randomly assigned to intravenous infusion of UFH (11 patients) or subcutaneous administration of enoxaparin (13 patients) were studied. The baseline clinical characteristics of each heparin-treated patient group are given in Table 1. No significant differences between the clinical characteristics of the two heparin-treated patient groups were found.

The mean values of plasma Fg, HMW-Fg, F1+2 and TAT before and at different time points of heparin treatment are reported in Table 2. At admission, patients in both treatment groups had significantly ($p < 0.001$) higher plasma Fg, HMW-Fg, F1+2 and TAT levels than normal subjects. During the 48 hours of heparin treatments the Fg, HMW-Fg, F1+2 and TAT levels remained significantly increased as compared to those in the control subjects ($p<0.05$ to $p<0.001$).

In comparison with the baseline levels, there was a significant increase in Fg ($p<0.05$) and HMW-Fg ($p<0.05$) in the two heparin-treated groups at 48 h. The F1+2 and TAT levels decreased in the two heparin-treated groups at the different times studied without significant differences. When the Fg, HMW-Fg, F1+2 and TAT values of the two groups of heparin-treated patients were compared, there were no significant differences in the Fg and HMW-Fg concentration and F1+2 and TAT levels at any time point (Table 2).

The mean plasma concentration of TF and vWF in the patients before and at different time points during UFH and enoxaparin treatments are reported in Table 2. Before heparin treatment, the TF and vWF

Table 2. Plasma hemostatic markers.

	Fg (mg/dL)	*HMW-Fg (mg/dL)*	*F1+2 (nmol/L)*	*TAT (µg/mL)*	*TF (pg/mL)*	*TFPI (ng/mL)*	*VWF (%)*
Baseline							
UFH	307±76	226±49	1.8±1	14.4±18	171±40	100±20	208±100
ENOX	308±75	224±60	2.0±0.9	15.3±17	167±39	101±38	199±68
6 h							
UFH	280±40	209±27	1.4±0.8	15.5±27	151±44	161±59#	188±72
ENOX	285±89	204±64	1.6±1.2	10.8±17	159±51	175±48#	164±66
12 h							
UFH	299±45	222±30	1.4±1.2	5.7±5.2	140±30	145±49*	199±82
ENOX	297±73	217±58	1.6±1.5	10.3±15	175±92	134±40*	170±70
24 h							
UFH	339±80	260±56	1.3±0.6	5.8±5	137±38	132±37*	222±107
ENOX	350±82	258±69	1.4±0.7	7.5±10	171±81	145±49*	188±56
48 h							
UFH	383±79*	307±52°	1.4±0.7	10.2±15	174±75	140±69	232±89
ENOX	375±83*	270±54*	1.5±0.6	11.2±15	185±75	140±70	194±54
Control	240±43	171±30	0.9±0.4	2.7±1.6	127±48	76±26	108±38

*Data are expressed as mean ± standard deviation. UFH, unfractionated heparin; ENOX, enoxaparin. Number of patients: UFH (n=11); ENOX (n=13). #p<0.001; °p<0.01; *p<0.05, vs. baseline.*

mean plasma levels were significantly higher in the two heparin treatment groups than in the control subjects (for UFH: TF, $p<0.01$; vWF, $p<0.001$ and for enoxaparin: TF, $p<0.02$; vWF, $p<0.001$). However, the plasma TF and vWF levels did not significantly differ from the baseline values at any of the time points. When the TF and vWF values of the UFH and enoxaparin treated groups were compared, there were no significant differences between these parameters at any time point (Table 2).

The mean plasma levels of TFPI in the UFH and enoxaparin groups are reported in Table 2. In comparison with levels in the control subjects, upon admission the patients assigned UFH (100±20 Vs 76±26 ng/mL, $p<0.01$) and those assigned enoxaparin (101±38 Vs 76±26 ng/mL, $p<0.02$) had significantly higher TFPI plasma levels. An increase of TFPI plasma levels was found at all the time points studied during heparin therapy ($p<0.001$). When the TFPI values of the two heparin-treated groups were compared with the TFPI values at baseline, there was a significant increase in TFPI plasma levels at 6, 12 and 24 hours ($p< 0.05$ to 0.001) in both heparin-treated patient groups (Table 2). However, after 48 hours of heparin treatment the TFPI levels were slightly but not significantly higher than those observed in the baseline blood samples. When the mean TFPI plasma values of the UFH and enoxaparin groups were compared, there were no significant differences at any time.

Discussion

Therapeutic control of prothrombotic states in ACS seems not to reduce thrombin generation, and activity continues even when therapeutic doses of heparin are used. The clinical advantages of enoxaparin over UFH in the management of ACS could be secondary to the higher anti-Xa activity of enoxaparin avoiding thrombin generation. In the present study, plasma hemostatic markers were measured in unstable coronary artery disease before and at different times during UFH or enoxaparin treatment.

The plasma baseline levels of F1+2 and TAT were higher in ACS patients than in control subjects. These observations are in agreement with results showing that plasma levels of thrombotic markers rise in the acute thrombotic phase of an unstable coronary syndrome.[1,17,21,22] During the 48 hours of heparin treatment, thrombin generation, as measured by F1+2 and TAT, tended to decline, although it remained higher than in control subjects despite treatment with UFH and enoxaparin. A similar reduction in the plasma levels of acute thrombotic markers was observed in UFH- and enoxaparin-treated patients in the ESSENCE study[17] and in dalteparin-treated vs. placebo-treated patients in the FRISC study.[22]

The plasma levels of Fg and HMW-Fg were elevated in our patients upon admission and these levels increased further over the first 48 hours despite UFH or enoxaparin treatment, thus showing the presence of an ongoing inflammatory process.[23-25]

Ours findings regarding the increased baseline plasma levels of vWF confirm that the first hours of evolving unstable coronary artery disease are associated with a significant acute-phase response.[23,25] Another finding of our study is that UFH and enoxaparin have a similar effect on vWF levels. However, at 48 h a slightly but not significantly higher vWF level was observed in UFH-treated patients than in those treated with enoxaparin. It has been reported[23,26] that vWF increases in unstable coronary artery disease patients treated with UFH over 48 h, whereas this response is blunted in patients receiving enoxaparin. The difference between these results and ours may have been influenced by the dose-dependent effect of UFH, since a higher level of intravenous UFH was administered in our study and this may have had an effect on the vWF acute-phase response.

The thrombogenicity of atheromatous plaques and dysfunctional endothelial cells is strongly influenced by TF, which is considered the predominant *trigger* for pathologic arterial thrombosis. Our patients had high plasma concentrations of TF at baseline. During the first 24 hours of UFH administration and after 6 hours of enoxaparin treatment the mean TF plasma levels were slightly but not significantly lower than those observed at baseline. These findings are in keeping with recent studies that demonstrated elevated plasma TF levels in patients with unstable angina[27-29] and that *in vivo* heparin administration caused a reduction in TF plasma levels.[28] This heparin-decreased TF may be due not only to a direct effect on cellular production but also an increase in heparin-induced TFPI. The contribution of TF to intravascular thrombotic events among individuals with advanced atherosclerotic coronary artery disease suggests that natural thromboresistance pathways, particularly TFPI, are of vital importance.[30,31] In our patients, the increase in TFPI antigen release was similar in those treated with UFH or enoxaparin. After 6 hours of treatment maximal TFPI release was observed in both heparin-treated groups. However, TFPI release decreased over time, which indicates that contin-

ued treatment with UFH and enoxaparin causes a progressive decrease in heparin-releasable TFPI. It has been reported that during 24-h continuous infusion of UFH in healthy subjects, TFPI-free release decreased but remained higher than the basal values.[32] Our study shows that heparin-releasable TFPI is depleted both during repeated subcutaneous injection of enoxaparin and during continuous intravenous infusion of UFH. These findings suggest a partial depletion of intravascular pools of TFPI by continuous heparin administration and may indicate that the constitutive synthesis of TFPI is surpassed by its elimination under these conditions.

In conclusion, when we evaluated the results obtained with UFH and enoxaparin in the management of ACS, we found no differences in plasma hemostatic markers during the 48 hours studied. Markers of thrombin generation, endothelial function and acute phase reaction manifest a similar response to UFH and enoxaparin. Thus, despite treatment with a high dose of UFH or enoxaparin an increase in thrombin generation may be a result of persistently activated inflammatory and endothelial processes, as observed in the present study.

Contributions and Acknowledgments

VV, VM and ER contributed to the conception and design of the study, carried out part of the analytical assays and contributed to the analysis and interpretation of the results. EP and FP were involved in the clinical management of the patients. MG contributed to the conception and design of the study, approved the protocol and revised its development. JA critically corrected the different versions of the manuscript. The order in which the names appear is based on the time spent by each contributor to this research. The authors wish to thank Guadalupe Manzano, Aurelia Royo, María Teresa Climent and Rosa Ferrer for their expert technical assistance.

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Disclosures

Conflict of interest: none.

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Potential implications for clinical practice

Despite treatment with unfractionated heparin or enoxaparin an increase in thrombin generation may be a result of a persistent activated inflammatory and endothelial process (see also recent papers in this journal on heparin therapy)[33-36]

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