

Use of a Combination of Enoxaparin or Unfractionated Heparin and Abciximab During Percutaneous Coronary Interventions: a Randomized Pilot Study

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Objectives. The cumulative experience gleaned from the NICE trials suggests that adjunctive enoxaparin therapy for percutaneous transluminal coronary angioplasty (PTCA), with or without concomitant abciximab therapy, is both safe and effective. However, no randomized studies have been conducted to compare the two strategies. The aim of this study was to evaluate the safety of combined enoxaparin-abciximab compared with standard therapy using unfractionated heparin and abciximab.

Patients and method. Ninety-nine patients undergoing PTCA were randomly assigned to receive either enoxaparin (enoxaparin group, 50 patients, 0.75 mg/kg) or unfractionated heparin (UH group, 49 patients, 70 U/kg) in an intravenous bolus. Both groups received standard abciximab treatment. The aPTT, creatine kinase (CPK), MB, troponin I, hemoglobin, and platelet count were determined 5 h and 17 h after PTCA. Endpoints were major bleeding and clinical or biochemical in-hospital events.

Results. There was less major bleeding in the enoxaparin group than in the UH group (1 vs 4) but the difference was not statistically significant. There were no significant differences in the frequency of in-hospital clinical events. There was a lower increase in aPTT at 5 h in the enoxaparin vs UH group ($p = 0.02$). It was impossible to remove the introducer in 7 of the UH group patients due to aPTT > 60 s as opposed to 1 patient in the enoxaparin group. Post-procedural CK elevation occurred in 8.0% of the enoxaparin group and in 6.1% of the UH group ($p = \text{NS}$). No thrombocytopenia was observed in either group.

Conclusions. Combined enoxaparin-abciximab as an adjuvant therapy during PTCA was safe and associated with a low incidence of major bleeding, major ischemic in-hospital events, and post-procedural CPK elevation.

Key words: Coronary angioplasty. Heparin. Stent.

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Received 28 November 2001.
Accepted for publication 4 July 2002.

Utilización de enoxaparina o heparina no fraccionada en combinación con abciximab durante la intervención coronaria percutánea: estudio piloto aleatorizado

Introducción y objetivos. La experiencia acumulada en los estudios NICE sugiere que el uso de enoxaparina (con o sin abciximab asociado) en la angioplastia es seguro y eficaz. Sin embargo, no existe ningún estudio aleatorizado que compare ambas estrategias. El objetivo ha sido evaluar la seguridad de la estrategia enoxaparina-abciximab frente a heparina no fraccionada (HNF) HNF-abciximab en la ACTP.

Pacientes y método. Un total de 99 pacientes sometidos a ACTP fue asignado aleatoriamente a recibir enoxaparina en bolo intravenoso preprocedimiento (grupo enoxaparina, 50 pacientes, 0,75 mg/kg) o HNF (grupo HNF, 49 pacientes, 70 U/kg). Ambos grupos recibieron abciximab de manera estándar. Se determinaron el APTT, CPK, MB, troponina I, hemoglobina y recuento de plaquetas a las 5 y 17 h posprocedimiento. Las variables de estudio fueron: incidencia de hemorragia mayor, acontecimientos clínicos y elevación de los marcadores de necrosis miocárdica.

Resultados. Hubo menos hemorragias mayores en el grupo enoxaparina (1 frente a 4), aunque no fueron estadísticamente significativas. No hubo diferencias significativas en los acontecimientos clínicos hospitalarios. Se observó un menor incremento del APTT a las 5 h en el grupo enoxaparina frente al HNF ($p = 0,02$). En el grupo HNF fue imposible retirar los introductores a las 5 h en 7 pacientes debido a APTT > 60 s frente a uno en el grupo enoxaparina. Se apreció elevación de CPK posprocedimiento en el 8% del grupo enoxaparina y en el 6,1% en el grupo de HNF ($p = \text{NS}$). No se observó trombocitopenia en ningún grupo.

Conclusiones. La estrategia combinada enoxaparina-abciximab como terapia adyuvante en la ACTP es segura y está asociada a un bajo índice de hemorragias mayores, acontecimientos clínicos intrahospitalarios y elevación de CPK posprocedimiento.

Palabras clave: Angioplastia coronaria. Heparina. Stent.

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ABBREVIATIONS

UFH: unfractionated heparin.
LMWH: low molecular weight heparin.
ASA: acetylsalicylic acid.
ACT: activated coagulation time.
APTT: activated partial thromboplastin time.

INTRODUCTION

Unfractionated heparin sodium (UFH) and acetylsalicylic acid (ASA) have been the preferred antithrombotic treatments for acute coronary syndromes and coronary angioplasty.¹ Nevertheless, the advent of new antiplatelet medications (tienopyridine, glycoprotein IIb/IIIa inhibitors) and antithrombotics such as low-molecular-weight heparin (LMWH) has created the need for intensive study of these treatment interventions. LMWH has several potential advantages over UFH in its use in acute coronary syndromes and coronary angioplasty. The most studied LMWH in this context is enoxaparin, and as a result this drug is the most routinely used in the treatment of acute coronary syndromes without ST segment elevation. Nevertheless, although there are studies on the use of enoxaparin in coronary angioplasty, these studies were not randomized, and therefore, sufficient data does not exist on this topic. The goal of our study was to evaluate the efficacy of combination therapy with enoxaparin and abciximab vs combination therapy with UFH and abciximab as adjunct antithrombotic therapy in coronary angioplasty.

PATIENTS AND METHOD

Patients

Between June and December of 2000 we performed 150 coronary angioplasties with stent implantation at our center. We undertook a prospective, randomized, nonblinded study of 99 patients, 50 of whom were taking enoxaparin and 49 of whom were taking UFH. Random assignment to the 2 homogenous patient populations was strict, and was performed by the random numbers system contained in the informatics program EpiInfo version 6.04. The indication for angioplasty was an acute coronary syndrome without ST elevation in 41 vs 40 patients, acute myocardial infarction (AMI) with Q-wave in 2 vs 9 patients with a positive stress test for ischemia, and stable angina in 7 vs 0 patients in the enoxaparin group vs the UFH group. Patients excluded from the study were those who pre-

sented at the hemodynamic laboratory on anticoagulant therapy; in other words, those who had received enoxaparin 12 hours before or Sintrom® 48 hours before catheterization or who had been treated with glycoprotein IIb-IIIa inhibitors, and those who were in cardiogenic shock. Before beginning the procedure, all patients received a loading dose of intravenous (IV) AAS (500 mg). The patients randomly received an IV bolus of enoxaparin (0.75 mg/kg) or UFH (70 U/kg). All patients received an IV bolus of abciximab (0.25 mg/kg) followed by a 12-hour IV perfusion 12 h (0.125 µg/kg/minute up to a maximum of 10 µg/minute). We did not perform activated coagulation time testing (ACT), and we did not measure the anti-Xa activity in any of the patients. All patients received 500 mg of oral ticlopidine at the end of the procedure.

Angioplasty was performed in a standard manner via femoral percutaneous puncture. We used a 7 Fr introductory sheath in all patients which was removed after 6 hours if the activated partial thromboplastin time (APTT) was normal.

The study was approved by a local committee of our institution, and all patients signed an informed consent form before being included in the study.

Clinical follow-up

The patients were followed during their post-procedure hospital course. For all patients, we determined the creatinphosphokinase (CPK), MB isoenzyme of the CPK (CPK-MB), troponin I, hemogram, and cephaline time at 6 hours and on the morning after the procedure was performed. The sensitivity of the troponin I test was 0.01. The APTT was determined using the ACL Futura Plus system in a conventional manner. The control value was 35 seconds. An AMI following the procedure was defined as a CPK value more than 3 times greater than the upper limit of normal. Urgent revascularization was defined as an ACTP or urgent coronary bypass surgery as a result of recurrent ischemia. We considered a major hemorrhage to be that which resulted in death, intracranial or intraocular hemorrhage, or a decrease in concentration of serum hemoglobin greater than 5 g/dL (or >15% of the hematocrit value). A minor hemorrhage was defined as all significant hemorrhages that did not fit the classification as major (epistaxis, hematoma, macroscopic hematuria). We also evaluated decreases in serum hemoglobin of less than 5 g/dL and evaluated any serious coronary event during the hospital course. The principal concern in terms of safety was to document any hemorrhagic event or local serious vascular complication.

Statistical analysis

Statistical analysis of the data was performed with the SPSS 9.0 program (SPSS Inc.). The qualitative

data was expressed in absolute frequencies and percentages, and the quantitative data was expressed as mean and standard deviation. The comparison of quantitative data was made by using the Student *t* test or the U Mann-Whitney test depending on data distribution. All the statistical tests were considered two-tailed, and all values of $P < .05$ were considered significant. We performed multiple logistical regression analysis to evaluate the influence of the variables of the different clinical interventions in the success or failure in terms the safety of both treatment groups.

RESULTS

Clinical characteristics

The clinical characteristics of each group are presented in Table 1. The majority of the patients were men in both groups. The cardiovascular risk factors were similar for both groups, except in terms of arterial hypertension (AHT) which had a higher incidence (62%) in the enoxaparin group. A greater number of these patients had experienced a previous AMI group while taking sodium heparin. Nevertheless, when we performed a multiple logistical regression analysis, there was no statistical association with AHT or with the incidence of hemorrhages or vascular complications in either treatment group, with a 95% confidence interval (95% CI) of 0.35 to 13.3 and an *odds ratio* (OR)=2.18. With regard to the typical treatment of these patients before coming to the hemodynamic laboratory, it should be pointed out that 72% in the enoxaparin group and 79.6% of the UFH group took AAS. Ten percent of the enoxaparin group and 12.2% of the UFH group were being treated with ticlopidine because they could not tolerate aspirin. Twelve percent of the enoxaparin group and 20.4% of the UFH group were treated with subcutaneous LMWH during their hospital stay and before undergoing catheterization. In these patients, enoxaparin administration was suspended 12 hours before the procedure. These patients received the same dose of enoxaparin or UFH as the other patients. Three patients in the enoxaparin group and 1 patient in the UFH group received anticoagulant treatment with Sintrom®, which was suspended 48 hours before catheterization; the prothrombin time determined before catheterization was greater than 70% in the 3 patients. There was no significant difference in prior antithrombotic treatment between the groups. With respect to vasodilator treatment, we did not observe differences between the groups with regard to previous ingestion of beta-blockers, calcium antagonists, or angiotensive enzyme converting inhibitors, although the patients in the sodium heparin group had received more treatment with nitrates ($P=.053$). There also was no difference between groups in the prior ingestion of statins.

TABLE 1. Clinical characteristics of both groups

Group Clinical characteristics	Enoxaparin (n=50)	UFH (n=49)	P
Male sex	37 (74%)	34 (69.4%)	NS
Age	62±12	6±11	NS
AHT	31 (62%)	21 (42.9%)	.05
Diabetes	11 (22%)	15 (30.6%)	NS
Dyslipemia	28 (56%)	27 (55.1%)	NS
Smoking	28 (56%)	30 (61.2%)	NS
Previous AMI	31 (62%)	21 (42.9%)	.05
Previous bypass	3 (6%)	1 (2%)	NS
Previous ACTP	4 (8%)	2 (4.1%)	NS

Angiographic characteristics

The anterior descending artery was dilated in 29 patients (58%) in the enoxaparin group and in 25 patients (51%) in the UFH group; the circumflex artery was dilated in 17 patients (34%) of the enoxaparin group and in 15 patients (30.6%) in the UFH group; and the CD artery was dilated in 24 patients (48%) in the enoxaparin group and 19 patients (38.8%) in the UFH group; in 1 case in each group we dilated the internal mammary artery to the anterior descending artery bypass. There were no significant differences in the type of artery treated in each group and there were also no differences in the type of lesion: type A, 2% vs 2%; B1, 24% vs 18.4%; B2, 24% vs 20.4%; C, 16% vs 16.3% in the enoxaparin group compared with the UFH group, respectively. Angiographic thrombus was present in 24% of the enoxaparin group vs 20.4% (NS) in the UFH group. The success of the angiographic procedure in both groups was 98%.

Hospital course

Clinical data

The incidence of events while subjects were hospitalized shown in Table 2. One patient died in the hemodynamic laboratory upon probing with the guide catheter as a result of thrombosis of the entire left system. This was a very high risk patient who had a previous AMI, a repeat AMI 5 days previously with suc-

TABLE 2. Incidence of clinical events during the hospital stay

	Enoxaparin (n=50)	UFH (n=49)	P
Without complications	42	38	NS
Death	1	0	NS
No-fatal AMI	4	3	NS
Pseudoaneurysm	1	0	NS
Major hemorrhages	1	4	NS
Total	7	7	NS

TABLE 3. Analytical follow-up values

	Enoxaparin (n=50)	UFH (n=49)	P
First CPK	110±113	108±105	NS
Second CPK	168±266	1883±313	NS
First MB	6.9±8.1	6.2±6.2	NS
Second MB	10.5±18.4	10.4±15.2	NS
First troponin I	0.25±0.7	0.23±0.49	NS
Second troponin I	0.57±1.65	0.75±2.14	NS
First HB	13.5±1.5	13.9±1.2	NS
Second HB	13.2±1.6	13.2±1.6	NS
First platelets, thousands	234±58	224±61	NS
Second platelets, thousands	232±68	212±59	NS

cessful rescue angioplasty, and unstable post-AMI that could not be controlled with medical treatment, which was the rationale for the last catheterization. The incidence of nonfatal post-procedure AMI was similar in both groups. One patient in the enoxaparin group had a pseudoaneurysm. The incidence of major hemorrhage, although not reaching statistical significance, was higher in the UFH group than in the enoxaparin group (8.2% vs 2.0%). With respect to minor hemorrhages, there was a decrease in hemoglobin of less than 5 g/dL in 2 patients in the IV heparin group, although without hemodynamic repercussions. Following the procedure, 1 patient in the enoxaparin group and 4 patients in the UFH group had an episode of angina without ECG changes that were controlled with medical treatment. There were no acute or subacute occlusions and no patient required urgent revascularization after the procedure.

Analytical data

Cephaline time at 6 hours was significantly greater in the UFH group vs the enoxaparin group (44 seconds±22 seconds vs 36 seconds±8 seconds) ($P=.026$). In 7 patients in the UFH group it was impossible to remove the introductory sheath after 6 hours due to prolongation of the cephaline time (>60 seconds), vs the same event in only 1 in the enoxaparin group. There were no significant differences in the determination of myocardial necrosis markers or in the hemogram values after the procedure (Table 3). We did not observe any thrombocytopenia in either group.

DISCUSSION

The most important finding of our study is that ACTP can be performed in a safe manner, using enoxaparin and abciximab as adjunct therapy. Until the present, the typical treatment used for angioplasty and acute coronary syndromes has been ASA¹ and UFH. This treatment has primarily an inhibitory effect on the thrombin (IIa) vs LMWH, which has a greater inhibi-

tory effect on Xa factor action.²⁻⁴ The complex pharmacodynamics of UFH, which entail a selective interaction with the endothelial cells and a strong binding action to the plasma proteins, means that its half life varies as a function of the dose administered (generally it is less than 2 hours when administered IV) and also means that the dose-response is less predictable with this agent. The LMWH have a very weak affinity with endothelial cells, as well as weak binding action to plasma proteins;⁵ therefore, its half life is longer (2 to 4 hours if administered IV and 3 to 6 hours if administered subcutaneously). In addition, the bioavailability of UFH is 28.6% and that of LMWH is between 87% and 98.9%. This means that dosing according to patient weight would be effective and would not require monitoring.⁶ There are 2 clinical settings in which monitoring LMWH action would be recommended: in the presence of serious renal insufficiency and morbid obesity.

Hemorrhage is the most frequent complication with heparin treatment. With UFH, this is a result of inhibition of coagulation, damage to plaque function, an increase in capillary permeability, and the induction of thrombocytopenia.⁴ LMWH can produce fewer hemorrhagic complications because of its lesser inhibition of plaque function as it does not increase capillary permeability and it less frequently induces thrombocytopenia.^{7,8} In clinical trials, nevertheless, this benefit has not been clearly shown with LMWH with respect to UFH, and no differences have been observed in the incidence of major hemorrhages, although minor hemorrhages have been observed, mainly at the puncture site of the LMWH. In our study, the incidence of significant hemorrhage was greater in the UFH group than in the enoxaparin group, although it did not reach statistical significance probably due to the limited patient sample studied. No clinically relevant minor hemorrhage occurred, although in 2 patients in the UFH group there was an important decrease in serum hemoglobin (less than 5 g/dL). In cases of serious hemorrhage, the action of the UFH can be neutralized with protamine; although it only neutralizes 70% of the circulating LMWH, which may be sufficient to control the hemorrhage. Finally, thrombocytopenia is more frequent with UFH than with LMWH, although no such incidents occurred in our study.

Another important aspect of the study is the monitoring of treatments. The use of UFH during ACTP, although routine, is based on empirical data and on non-randomized studies.⁹ In addition, UFH continues to be used although consensus on optimum dose has not been reached with regard achieving an adequate anticoagulation level in patients subjected to ACTP. In the majority of hemodynamic laboratories, treatment with UFH is easily controlled with ACT. Nevertheless, treatment may be affected if other drugs are used in a concomitant manner, such as glycoprotein IIb-IIIa in-

hibitors; as a result, low doses of UFH are used when this type of drug is administered. The LMWH can be monitored by measuring anti-Xa factor activity; however, this measurement cannot be performed at bedside, as it requires complex techniques and specialized staff; besides, the more predictable dose-response of these heparins makes this control unnecessary. In our study we did not monitor either of the 2 treatment groups.

The majority of clinical trials that compare UFH with LMWH have been performed in the context of acute coronary syndrome without ST segment elevation. In these studies, the LMWH have been shown to be similar or superior to the efficacy of the UFH, which means that it is used routinely in clinical practice.¹⁰⁻¹⁶ We are aware of only one preliminary study and results that evaluated the usefulness LMWH in the hemodynamic laboratory, since it is still not clear when ACTP should be performed on patients who are being treated with subcutaneous LMWH. In a recent study,¹⁷ it was reported that stopping treatment with LMWH before catheterization (a practice followed in our center) is inconvenient and unnecessary if the catheterization is performed within 8 hours after the last LMWH injection; ACTP can be performed safely without the need for adding a new dose of LMWH or UFH. The enoxaparin dose was only adjusted according to the anti-Xa activity in older patients or patients with renal insufficiency. The introductory catheters were removed without incident 10 hours after the last injection of LMWH. In our study, the anti-Xa activity was satisfactory in 97.6% of patients who were treated in the hemodynamic laboratory. In our study, although 12% of patients in the enoxaparin group and 20% of the patients in the UFH group had had prior treatment with enoxaparin (1 mg/kg every 12 hours), we used a loading IV dose in the catheterization lab. Although this could have produced excessive anticoagulation in the patients in our study, of the patients involved in the 5 notable hemorrhagic episodes, only 2 had received previous treatment with subcutaneous enoxaparin. In the study by Collet et al,¹⁷ abciximab was used in only 9.2% of patients, in spite of the fact that it was a high-risk study population. Nevertheless, no acute occlusion or urgent revascularization was reported, as was the case in our study.

There is limited information available on the use of IV LMWH in ACTP; this is an area of growing interest. Small, early study results from comparisons of using LMWH with UFH have shown the safety of this intervention when it is performed in the hemodynamic laboratory.^{18,19} The NICE-1 (National Investigators Collaborating on Enoxaparin) pilot study²⁰ compared both strategies without the concomitant use of glycoprotein IIb-IIIa inhibitors. The study compared using an IV bolus of 10 000 units of UFH with using an IV bolus of 1 mg/kg of LMWH (enoxaparin) prior to ACTP. Although this was a small study (60 patients),

no differences were found in the clinical events or hemorrhages between the 2 groups. In another study, an enoxaparin intervention was tested in 827 consecutive patients and, at 30 days, 5.4% of the patients had experienced some type of clinical event and 1.1% of patients had experienced a major hemorrhagic event. The percentage of transfusions and severe thrombocytopenia was low; 2.7% and 0.2%, respectively. The NICE-4²¹ study was not randomized and included patients who received a percutaneously administered combination of enoxaparin (0.75 mg/kg) and abciximab (0.25 mg/kg) in an IV bolus immediately before the procedure, followed by a 12-hour perfusion of abciximab. The peri-procedure ACT was not monitored. It was determined that these patients could be compared to the patients in the low-dose (70 U/kg) UFH group from the EPILOG study.²² There was a very low incidence of hemorrhagic events requiring transfusion: 0.6% as compared with 2.7% in the EPILOG study. In the NICE-3 study, the incidence of major hemorrhages was similar when enoxaparin was combined with tirofiban, eptifibatide, or abciximab to the incidence already known to occur with UFH. In our study, the incidence of hemorrhage was greater than 2% in the enoxaparin group and 8.2% in the UFH group, using the same dose as in the NICE-4 and EPILOG studies. Of note, the number of hemorrhagic events in the NICE-1 study was greater than in the NICE-4 study, in which abciximab was used (3.2% vs 2.0%). In our study, the incidence of hemorrhagic events in the UFH group was higher than in any published reports at the present time for multicenter studies, in spite of the fact the same doses were used in those studies. On the other hand, the incidence of clinical events was greater in the NICE-1 study (7.9%) than in the NICE-4 study (2.8%), which was an expected result due to the benefit demonstrated by abciximab. In our study, the incidence of the combined clinical events of death and AMI was 10% in the enoxaparin group and 6% in the UFH group. This high incidence rate is a result of, above all, the peri-procedure enzyme elevation. In the EPISTENT study,²³ the incidence rate for these combined events was 4.8%, similar to that of the UFH group in our study. The higher percentage in the LMWH group a result of the fact that in this group death occurred in one high-risk patient and, therefore, is not a result of the use of antithrombotic drugs but to the more high-risk profile of the patients in this group.

As expected, the APTT at 6 hours was more prolonged in the UFH group than in the enoxaparin group. LMWH has little effect on the prolongation of APTT. In 7 patients in the UFH group, the introductory catheter could not be removed 6 hours after the procedure due to APTT prolongation (>60 seconds). This also occurred in a patient from the enoxaparin group, but this could have been due to a laboratory error. With the rest of the analytical tests performed in our study

there were no significant differences between patients, including in plaque recounts.

Study limitations

This was a pilot study and therefore the patient sample is small for extracting definitive conclusions. In addition, although it was a randomized study, it was not blinded, which may have introduced some skew in patient selection. It is important to know in detail the studies performed but not yet published that have used this intervention, and to perform an extensive multicenter study, randomized, that uses this intervention (enoxaparin plus abciximab) routinely as an adjunct therapy for ACTP; this study would need to include results of monitoring in the hemodynamic laboratory when LMWH are used.

CONCLUSION

The combination of enoxaparin and abciximab as an adjunct treatment for ACTP in this randomized pilot study was safe and was associated with a low occurrence of major hemorrhages, clinical events, and periprocedure CPK elevation. In addition, it allowed the removal of introductory catheters 6 hours after the procedure with total safety and without the need for previous monitoring. The advantages of this strategy vs the traditional interventions need to be evaluated in an extensive clinical trial before being routinely incorporated into clinical practice.

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