Clinical Research

Comparison of Enoxaparin and Unfractionated Heparin in Coronary Angioplasty

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Introduction: Recent studies have shown that enoxaparin may be equally as safe and effective as unfractionated heparin during a coronary angioplasty procedure. The aim of this study was to investigate whether enoxaparin can be used effectively and safely in place of unfractionated heparin in patients undergoing emergency or programmed coronary angioplasty, regardless of the use of platelet glycoprotein IIb/IIIa inhibitors.

Methods: We compared two series of consecutive patients, who received unfractionated heparin (n=217) or enoxaparin (n=116) during emergency or programmed angioplasty, regardless of age, weight, renal function and the coadministration of platelet glycoprotein IIb/IIIa inhibitors. In the patients who received enoxaparin the arterial sheaths were removed immediately after the procedure.

Results: There were no significant differences between the two groups as regards clinical characteristics or risk factors for coronary artery disease. During a 30-day follow up no major adverse cardiac events were observed (death, myocardial infarction, target vessel revascularisation). Multivariate logistic regression analysis showed no correlation between the anticoagulant used and the occurrence of major cardiac events in the two groups of patients (log odds ratio= -9.46, p=0.89), after controlling for age, sex, administration of platelet glycoprotein IIb/IIIa inhibitors, number of coronary lesions, number of stents used, clinical picture and risk factors for coronary artery disease. As regards the development of haematoma in the groin, the only significant independent predictive factor for this was the coadministration of platelet glycoprotein IIb/IIIa inhibitors.

Conclusions: The use of enoxaparin in coronary angioplasty is safe, effective and allows faster removal of sheaths and mobilisation of the patient.

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Although unfractionated heparin has been for a long time the antithrombotic treatment of choice during coronary angioplasty,[1,2] recent studies have showed that the intravenous administration of enoxaparin is equally safe and effective and offers advantages over unfractionated heparin in terms of a shorter hospital stay.[3-7] In the NICE 4 and NICE 1 studies[3] the administration of enoxaparin during angioplasty, with or without the coadministration of abciximab, was found to be safe, with a low haemorrhagic risk. More recently, the NICE 3 study extended this observation to the combination of enoxaparin with tirofiban or eptifibatide.[6] In practice these studies involved the recording of data and experiences from series of patients that were not randomised. One pilot study[8] used randomisation in comparing intravenous enoxaparin with unfractionated heparin during angioplasty, and found similar success and complication rates. However, the latter study was small (60 patients) and only a small minority of patients received stents. The CRUISE study, which was the first large, randomised study of enoxaparin versus unfractionated heparin in combination with eptifibatide, confirmed the safety and efficacy of enoxaparin, but only when linked

with the coadministration of platelet glycoprotein IIb/IIIa inhibitors.[9] Experience to date is thus based on only a small number of studies.

Here we report our experience from two consecutive series of patients who were treated either with unfractionated heparin or with enoxaparin during programmed or emergency angiography, regardless of whether or not platelet glycoprotein IIb/IIIa inhibitors were given.

Methods

Patients

Two hundred and seventeen consecutive patients who were undergoing programmed or emergency coronary angioplasty in our haemodynamic laboratory were given intravenous unfractionated heparin (100 IU/Kg bolus with supplementary doses of 10-20 IU/Kg until an activated coagulation time, ACT, >250 s was achieved). In patients who were also receiving a platelet glycoprotein IIb/IIIa inhibitor the initial bolus dose of heparin was 60 IU/Kg and the target ACT was 200-250 s. Another 116 consecutive patients undergoing emergency or programmed coronary angioplasty were given intravenous enoxaparin (1 mg/Kg, or 0.75 mg/Kg if a platelet glycoprotein IIb/IIIa inhibitor was given). All patients were taking aspirin and ticlopidine or clopidogrel, whose administration had started before the patients came to the laboratory. All patients with an acute coronary syndrome had been given a platelet glycoprotein IIb/IIIa inhibitor in the standard dosage,[10] while in the remaining patients this treatment was left to the discretion of the physician performing the catheterisation. Angioplasty was performed in all patients in the standard way, via a femoral approach. In the patients who received unfractionated heparin the arterial sheath was removed 4 hours after the last heparin dose was administered, provided that the ACT had reduced to <150 s, whereas in the patients who were given enoxaparin the sheath was removed immediately after completion of the angioplasty. All patients were mobilised 6 hours after removal of the sheath. All were monitored for at least 6 hours and any complications were noted (death, myocardial infarction, acute thrombosis and vessel occlusion, haemorrhage or other vascular complications). After the patients were discharged from hospital all similar events were recorded during a 30-day period.

Definitions

Haemorrhagic complications included a reduction in haemoglobin >3 g/dl, need for blood transfusion, or any systemic haemorrhage or significant haemorrhage from the cannulation site. Vascular complications were classified as major (vascular damage requiring surgical repair, arteriovenous communication or pseudoaneurysm or development of haematoma after angioplasty that was accompanied by a significant reduction in haemoglobin and haematocrit and that needed medical intervention or prolonged pressure in order to stop the haemorrhage) and minor (creation of a stable haematoma at least 5 cm in diameter that did not increase in size, serious vasovagal reaction).

Statistical analysis

All continuous variables are expressed as mean ± standard deviation. Qualitative variables are given as absolute and relative frequencies. Contingency tables with the χ^2 method were used to assess differences between the two groups (unfractionated heparin versus enoxaparin) and in the remaining qualitative variables. Student's t-test was used to evaluate correlations between the study groups and the patients' age. The Mann-Whitney test was used to assess and recognise differences between the two groups in relation to continuous non-parametric variables. Logistic regression analysis was used to assess whether enoxaparin treatment was as safe as treatment with unfractionated heparin. The size of the groups was sufficient to examine the null hypothesis with a 10% difference in the clinical complications between the two study groups, with 5% probability and 80% statistical power. The SPSS 8.0 (SPSS Inc., USA) software package was used for the statistical analysis.

Results

Patients

Tables 1 and 2 show the clinical characteristics of the patients and details related to the procedures. There was no statistically significant difference between the two groups as regards clinical characteristics or the presence of cardiovascular risk factors. The frequency of platelet glycoprotein IIb/IIIa inhibitor administration was significantly higher in patients of the enoxaparin group. Two patients of the enoxaparin group and 5 from the unfractionated heparin group had high creatinine levels (>1.5 mg/dl). Although stents were used frequently in both groups, the numbers of stents per patient and stents per lesion were significantly greater in the enoxaparin group.

Table 1. Clinical characteristics of the patients.

	UFH	Enoxaparin	p
No. of patients	217	116	
Men (n, %)	205 (94.5%)	104 (89.7%)	0.1
Age (years)	56.9 ± 10.7	54.8 ± 11.3	0.098
Stable angina (n, %)	69 (31.8%)	25 (21.6%)	0.048
Unstable angina (n, %)	120 (55.3%)	71 (61.2%)	0.29
Asymptomatic (n, %)	28 (12.9%)	20 (17.2%)	0.28
Three-vessel disease (n, %)	50 (23%)	27 (23.3%)	0.96
Previous myocardial infarction (n, %)	103 (47.5%)	57 (49.1%)	0.77
Ejection fraction <40% (n, %)	38 (17.5%)	15 (12.9%)	0.275
Serum creatinine >1.5 mg/dl	5 (0.02%)	2 (0.01%)	0.72
Hypertension (n, %)	127 (58.5%)	61 (52.6%)	0.298
Dyslipidaemia (n, %)	199 (91.7%)	111 (95.7%)	0.172
Diabetes mellitus (n, %)	35 (16.1%)	24 (20.7%)	0.299
Smoking (n, %)	157 (72%)	88 (76%)	0.318

UFH: unfractionated heparin

Table 2. Details related to the angioplasty procedure.

	UFH	Enoxaparin	p
Platelet glycoprotein IIb/IIIa inhibitors (n, %)	96 (44.2%)	110 (95.7%)	<0.001
Lesions per patient	1.33 ± 0.57	1.59 ± 0.85	0.007
Stents per patient	0.86 ± 0.65	1.25 ± 0.88	<0.001
Stents per lesion	0.64 ± 0.47	0.78 ± 0.4	<0.001
Total stents implanted	188	146	
Total coronary lesions	290	185	

UFH: unfractionated heparin

Major adverse cardiac events

There were no deaths, myocardial infarctions, acute vessel occlusions or major haemorrhages during the procedure or immediately after the patients left the laboratory. There was a statistically significant difference in the occurrence of periprocedural complications between the unfractionated heparin group and the enoxaparin group (0.0% versus 2.6%, respectively, $\chi^2=5.6$, p=0.05). Regarding major complications, in the enoxaparin group 1 patient (0.8%) had a transient ischaemic cerebral episode 24 hours after the angioplasty and 1 patient (0.8%) developed a haematoma at the cannulation site, which required prolonged pressure application and extended the patient's hospital stay by a day. In the unfractionated heparin group 2 patients had a severe vasovagal reaction during removal of the arterial sheaths, which necessitated the administration of large quantities of fluids, atropine and epinephrine (minor complications) (Table 3).

In spite of the above, the univariate regression analysis that was carried out in order to investigate whether enoxaparin was a predictor of periprocedural complications revealed that neither treatment was a prognostic factor for major clinical complications during the procedure or immediately afterwards (difference in adverse cardiac events: 10%, log odds ratio: -9.5, p: 0.85). The administration of platelet glycoprotein IIb/IIIa inhibitors was also unrelated to the incidence of major periprocedural complications (p=0.85). Furthermore, multivariate logistic regression analysis showed no correlation between the occurrence of major periprocedural complications and the anticoagulation treatment used (log odds ratio: -9.46, p: 0.89), after correction for age, height, platelet glycoprotein IIb/IIIa inhibitor administration, number of coronary lesions, number of stents implanted, clinical picture and risk factors for coronary artery disease.

During 30-day follow up no patients of either group suffered any major adverse cardiac event (death, myocardial infarction or subacute thrombosis).

Minor complications

Ninety-six patients (82.7%) in the enoxaparin group and 108 (49.7%) in the unfractionated heparin group

Table 3. Adverse cardiac events.

	Enoxaparin (n=116)		UFH (n=217)	
Adverse event	With IIb/IIIa (n=111)	Without IIb/IIIa (n=5)	With IIb/IIIa (n=96)	Without IIb/IIIa (n=121)
Transient cerebrovascular event	1 (0.8%)	0	0	0
Serious vasovagal episode	0	0	1 (1%)	1 (0.8%)
Major haematoma	1 (0.8%)	0	0	0
Stable, non-expanding haematoma	95 (85.5%)	1 (20%)	84 (87.5%)	24 (19.8%)

UFH: unfractionated heparin

had a stable, non-deteriorating haematoma, which was seen on the first re-examination after discharge, 5-7 days after angioplasty. This occurred mainly in patients treated with platelet glycoprotein IIb/IIIa inhibitors (Table 3).

Univariate logistic regression analysis showed that the appearance of a stable, non-expanding haematoma after sheath removal was correlated significantly with the use of enoxaparin (odds ratio: 4.8, 95% CI:2.79-8.37, p<0.00009) and the administration of platelet glycoprotein IIb/IIIa inhibitors (odds ratio: 25.8, 95% CI:14.28-46.68, p<0.00009), but had no relation with sex, age, elevated serum creatinine levels, diabetes, hypercholesterolaemia, hypertension or smoking history. However, multivariate logistic regression analysis showed that the only significant independent prognostic factor for the appearance of a stable haematoma was the coadministration of platelet glycoprotein IIb/IIIa inhibitors (odds/ratio: 33.6, 95% CI:15.46-73.17, p<0.00009). The other factors examined were unfractionated heparin versus enoxaparin (p=0.38), sex, age, elevated creatinine levels (>1.5 mg/dl) and the existence of classical risk factors for coronary artery disease.

Discussion

There are already reliable indications suggesting that low molecular weight heparin could replace the standard unfractionated heparin in many clinical situations.[11] However, the use of enoxaparin in coronary angioplasty and the appropriate antiplatelet treatment following the procedure are still under discussion.[12]

Choussat et al[3] showed that a small dose of intravenous enoxaparin (0.5 mg/Kg) was safe and effective and needed no alteration in dosage when coadministered with eptifibatide in programmed angioplasties. However, in that study the sheaths were removed 4 hours after the procedure in the patients who were given eptifibatide. In our study we have shown that even intravenous doses of enoxaparin >1 mg/Kg or 0.75 mg/Kg given with the simultaneous administration of platelet glycoprotein IIb/IIIa inhibitors during programmed or emergency angioplasty are equally as safe as the standard unfractionated heparin and allow the immediate removal of the sheath after the patient leaves the laboratory, with no increase in vascular complications.

Moliterno et al showed that a prolonged ENOX time (a method for evaluating the anticoagulant effect of enoxaparin) at the time of arterial sheath removal was correlated with an increase in haemorrhagic complications.[13] In our study we did not monitor the anticoagulant effect. However, administration of the same dosage pattern to our patients did not result in any increase in major periprocedural complications or major adverse cardiac events in the patients receiving enoxaparin. Sheath removal immediately after angioplasty in the enoxaparin group also did not lead to any major complications, but rather helped to mobilise the patients sooner and reduced their time in bed following the procedure. Although the coadministration of platelet glycoprotein IIb/IIIa inhibitors was more common in the enoxaparin group, there was no significant increase in the incidence of haemorrhage or the appearance of significant haematomas compared to the unfractionated heparin group. Also, there was no greater incidence of subacute in-stent thrombosis, even though stents were used more widely in the enoxaparin than in the unfractionated heparin group. Furthermore, no patient in the enoxaparin group had a vasovagal reaction on removal of the sheath.

A recent systematic analysis of randomised studies comparing enoxaparin with standard unfractionated heparin in patients with acute coronary syndrome showed that enoxaparin was more effective in reduc-

ing 30-day death and myocardial infarction rates after the procedure, without increasing the incidence of haemorrhagic complications.[14] Another study of acute coronary syndrome patients who were classified as high risk and were treated with immediate angioplasty found that the administration of enoxaparin was safe and effective, was associated with a moderate increase in haemorrhagic complications, but was more practical in use.[15]

In our study age did not affect the patients' clinical course or the appearance of complications. The fact that elevated serum creatinine levels (>1.5 mg/dl) lacked any prognostic significance for the appearance of complications in the patients of this study should be interpreted with caution, because of the small number of patients with diminished renal function. However, Kereiakes et al[12] reported in a recent publication that the dosage of low molecular weight heparin needs to be modified only in cases of severe renal failure.

We observed a difference between univariate and multivariate regression analysis in relation to the administration of unfractionated heparin or enoxaparin as a prognostic factor for non-deteriorating haematoma after sheath removal. This could be attributed to the fact that the administration of platelet glycoprotein IIb/IIIa inhibitors was more frequent in the enoxaparin group. Small haematomas in the groin region were seen in the majority of the patients given enoxaparin, especially when a platelet glycoprotein IIb/IIIa inhibitor was also given. According to our experience, the early removal of the sheath when the patient has been given enoxaparin during the procedure, apart from being practical for both doctor and patient, may certainly give rise to the appearance of a small haematoma, which disappears over the next few days and causes the patient no significant discomfort.

Limitations of the study

This study was not randomised and compared the outcome of consecutive series of patients who underwent programmed or emergency coronary angioplasty with the use of enoxaparin to those who were given standard unfractionated heparin. Although there were no statistically significant differences between the groups as regards clinical characteristics, it must be borne in mind that there were such differences in relation to the extent of the coronary artery disease, the number of stents implanted and the administration of platelet glycoprotein IIb/IIIa inhibitors.

Conclusions

Enoxaparin in doses of 1 mg/Kg, or 0.75 mg/Kg when given together with platelet glycoprotein IIb/IIIa inhibitors, can be substituted for the administration of standard unfractionated heparin in both emergency and programmed angioplasty. Enoxaparin offers similar efficacy to unfractionated heparin, without increasing the risk of haemorrhage or causing other side effects, and allows removal of the sheath immediately after the patient leaves the laboratory, thus speeding up the patient's mobilisation. We believe that enoxaparin could replace unfractionated heparin in daily clinical practice in the haemodynamic laboratory.

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