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Prevention of Postoperative Venous Thrombosis: A Randomized Trial Comparing Unfractionated Heparin with Low Molecular Weight Heparin in Patients Undergoing Total Hip Replacement

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Key words

Low molecular weight heparin – Postoperative thrombosis – Total hip replacement

Summary

A double blind randomized trial comparing subcutaneous enoxaparin (40 mg once daily) with standard unfractionated calcium heparin administered at a dose of 5,000 units every 8 hours in patients undergoing elective hip replacement has been performed. Treatment regimens began 12 hours preoperatively with enoxaparin, 2 hours preoperatively with standard unfractionated calcium heparin, and were continued for 15 days or until discharge. Venography was performed in all patients. Two hundred thirty-seven patients were included in the study: 113 received unfractionated heparin and 124 received enoxaparin. The incidence of proximal deep vein thrombosis was reduced from 18.5% in the unfractionated heparin group to 7.5% in the enoxaparin group ($p = 0.014$), and the incidence of total deep vein thrombosis was similarly reduced from 25% to 12.5% ($p = 0.03$). There were two major bleeding episodes and one minor bleed in the enoxaparin group compared to two minor bleeds in the unfractionated heparin group. Patients who received enoxaparin required fewer red blood cell transfusions and had a significantly higher hemoglobin on postoperative days 3 and 4. Thus prophylaxis with enoxaparin, 40 mg once daily, is simple, safe and more effective than standard low dose unfractionated heparin in preventing deep vein thrombosis in patients undergoing elective hip replacement.

Introduction

A number of low molecular weight (LMW) heparins have been evaluated in clinical trials. Today, the safety and efficacy of a LMW heparin in patients undergoing hip surgery have only been demonstrated in a single study (1). We have previously compared a once daily dose of 40 mg of enoxaparin, LMW heparin, with 20 mg of enoxaparin administrated twice daily. In patients undergoing total hip replacement both regimens which were administered subcutaneously 12 hours before surgery appeared to be relatively safe and effective (2, 3).

A number of studies have evaluated unfractionated standard heparin as prophylaxis in patients undergoing elective hip surgery (4–11). Although, the results of these studies were not all consistent, the majority demonstrated clinical benefit in favour of heparin (4–9). Nonetheless, prophylaxis with standard heparin is not widely used in patients undergoing elective hip surgery, because of the concern for bleeding and doubt of its effectiveness among orthopedic surgeons.

There is evidence from experimental studies in animals that LMW heparin produces less hemorrhage for an equal antithrombotic effect than standard unfractionated heparin and higher heparin blood levels as measured by anti-factor Xa levels can be achieved without an increased hemorrhagic risk (12). Thus the increase in the therapeutic margin could potentially be advantageous in patients undergoing elective hip surgery. We therefore, elected to compare LMW heparin with standard unfractioned calcium heparin, 5,000 IU 8 hourly, in patients undergoing total hip replacement.

Patients, Materials, and Methods

Patients

Orthopedic surgeons in seven hospitals took part in the study. In each centre, consecutive patients, who were 45 years of age or older, and who were undergoing elective hip replacement were studied.

Patients were excluded if they had an underlying bleeding disorder, a history of allergy to iodine or radiopaque dye, renal insufficiency, with a creatinine greater than 30 mg/l; a history of deep vein thrombosis associated with previous hip surgery, if they had undergone previous hip replacement of the same hip, or if they had taken anticoagulant or antiplatelet therapy during the 8 days prior to surgery. Patients with previous venous thrombosis were excluded because such patients have a particularly high risk of recurrence. Patients with previous hip replacement were excluded because they could have had silent thrombosis, and so, would have been at a high risk for recurrence. All exclusions were documented. Concurrent treatment with vitamin K antagonists, aspirin or other platelet inhibitors, non steroidal anti-inflammatory drugs or dextrose, was not permitted. Informed consent was obtained from all eligible patients.

Patients were operated on at 8 a.m., under general anesthesia, without controlled hypotension. All patients received the same physical methods for prophylaxis which included elevation of the foot of the bed, early ambulation, and elastic bandaging of the legs.

Regimens

The patients received treatment with either enoxaparin 40 mg daily or unfractionated heparin 5,000 IU 8 hourly, both administered subcutaneously for 14 days or hospital discharge if earlier. Medications were dispensed into identical syringes in unit doses of 0.2 ml. Injections commenced 12 hours before surgery. To maintain double blinding each patient received two injections, the evening and morning before surgery, then three injections every 8 hours, at 6 a.m., 2 p.m. and 10 p.m. In the enoxaparin group, patients received enoxaparin at 10 p.m. and two injections of saline placebo at 6 a.m. and 2 p.m. while for the unfractionated heparin group patients received a placebo injection the

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Table 1 Clinical characteristics of the two study groups

	Enoxaparin group	Heparin group
Patients included	124	113
Patients analysed	124	112
Sex Men	61	45
Women	63	67
Age (mean years ± sd)	65.4 ± 9.1	66.3 ± 9.4
Weight (kg mean ± sd)	69.1 ± 13.4	65.3 ± 12.5
Height (meters mean ± sd)	1.64 ± 0.07	1.62 ± 0.08
Previous or present risk factors:		
– Oestroprogestative treat.	1	1
– Varicose veins	31	33
– Varicose ulcers	3	2
– Obesity	43	27
– Hyperlipidemia	30	23
– Preop. confinement to bed 2 days or more	1	7
– Infection in other site	4	7
– Cardiopathy	30	28
– Arterial hypertension	40	41
– Chronic bronchitis	17	15
– Leg paralysis	1	0
– Functional impairment	46	41
– Previous orthopedic surgery	44	33
– Previous gynecologycal surgery	36	33
Surgical interventions:		
– Operated side Right	65	55
Left	59	57
– Duration anesthesia (min)	138.9 ± 78.3	141.9 ± 73.2
– Duration intervention (min)	63 ± 30	66 ± 23

night before surgery (10 p.m.) and then unfractionated heparin at 6 a.m., 2 p.m. and 10 p.m.

Enoxaparin (PK 10169, Pharmuka Laboratories, Gennevilliers, France), was prepared by partially controlled depolymerization of the benzylic ester of porcine mucosal heparin. The mean molecular weight is between 4,000 and 6,000 daltons and the concentration was 200 mg/ml. Standard calcium heparin was prepared from porcine mucosal heparin and had a specific activity of 160 to 180 IU/mg.

Blood was collected at 10 a.m. for all patients (12 hours after the injection of enoxaparin and 4 hours after unfractionated heparin) into 0.110 M citrate (1 vol. 3.8% trisodium citrate + 9 vol. blood). The blood was centrifuged at 3,000 rpm for 15 minutes at room temperature. Plasma heparin was assayed daily by a chromogenic anti-factor Xa method using the Stachrom heparin assay (Stago, ASNIERES) modified for use on a RA 1,000 analyser (Technicon, DORNANT). Three hundred and fifty microliters of bovine factor Xa was added to 30 µl of plasma, and incubated for 150 seconds at 37° C. Then 100 µl of CBS 31.39 chromogenic substrate (STAGO) was added. The reaction was monitored at 405 nm after 60 seconds. The absorbance results were plotted against the standard low molecular weight heparin (PK 10169) curve. This PK 10169 standard has been recently assayed against the International Low Molecular Weight Heparin Standard and the anti-factor Xa activity was found to be 100 IU/mg.

Outcome Measures

Venous thrombosis. Venous thrombosis was diagnosed by bilateral ascending phlebography which was performed between day 12 and day 15 post operatively or earlier if symptoms or signs suggestive of deep vein thrombosis (DVT) or pulmonary embolism (PE) occurred.

The venograms were interpreted by a central committee of three radiologists independently without knowledge of the treatment assignment.

Venous thrombosis was diagnosed when phlebography revealed a constant intraluminal filling defect in a deep vein (13) and classified as proximal if the thrombus was in the popliteal or more proximal vein, or distal, if the thrombus was in the calf veins. If a patient had both proximal and distal venous thrombosis they were classified as having proximal DVT. Patients found to have DVT were treated by standard methods.

Patients were examined daily for evidence of wound hematoma and other signs of hemorrhage. The bleeding was classified as major if it was overt and associated with either a fall in hemoglobin level of 2 g/dl or more or a need for transfusion of two or more units of blood, or if it was retroperitoneal or intracranial. Bleeding was defined as minor if it was overt but did not meet the other criteria for major bleeding (14). All bleeding episodes were reviewed by a central committee unaware of treatment allocation.

The number of units of blood transfused during and after the operation, the level of hemoglobin (Hb), hematocrit (Ht) and the blood platelet count were recorded pre-operatively and then post-operatively on days 1, 3 or 4, 6 or 7, 10, and on the day of discharge.

Statistical Analysis

The sample size estimation was based on the assumption that approximately 30% of patients receiving heparin and 10% of patients receiving enoxaparin would develop postoperative DVT. Based on these considerations, an alpha of 0.05 (two-tailed) and a power of 80%, it was calculated that 98 patients per group would be required to detect a difference of this magnitude.

Comparisons of the rates of DVT and bleeding where performed using the chi squared statistic with continuity correction. Daily hemoglobin measurements, transfusions requirements, and anti-factor Xa levels were compared by using analysis of variance procedures with repeated measures.

Results

Study Population

493 consecutive patients were considered for the study; 256 were excluded for the following reasons: bleeding disorder, 10; allergy to iodine or radiopaque dye, 15; history of deep vein thrombosis with previous hip surgery, 65; a previous hip replacement on the same hip, 98; treatment with anticoagulants or antiplatelet agents at the time of referral, 23; renal insufficiency, 9; refusal to provide informed consent, 17; other miscellaneous causes, 19.

Of the 237 patients randomized, 113 received unfractionated heparin and 124 received enoxaparin. The treatment groups did not differ significantly within centres or between centres in the following baseline characteristics: sex, age, weight, height, previous or present risk factors, the side of the operation, or type of surgery (Table 1).

In the unfractionated heparin group, one randomized patient was excluded from the study because a rash which developed immediate preoperatively prevented the patient from going to surgery. In addition two patients refused phlebography after they had initially accepted, and in two patients phlebography could not be performed because of technical difficulties. Therefore, the safety analysis was performed in 112 patients and efficacy was analysed in 108 patients.

In the enoxaparin group, one patient was considered ineligible at the time of surgery because he had a fracture of the femur and required extensive surgery. Three patients did not have phlebography performed; two refused, and one had an iodine allergy. Therefore, the efficacy analysis was based on 120 patients. All patients who did not have phlebograhy performed were carefully followed up at 1 and 6 months; none developed clinical evidence of DVT or PE.

Seventy-nine patients in the heparin group, had a cemented total hip replacement, and 29 had a non-cemented arthroplasty. In the enoxaparin group, 77 patients had a cemented total hip replacement and 43 had a non-cemented arthroplasty.

Frequency and Distribution of Thrombosis (Table 2)

Phlebography was performed on day 12.1 ± 1.7 in the enoxaparin group, and on day 11.7 ± 2.0 in the heparin group.

Of the 120 patients in the enoxaparin group, DVT was detected in 15 patients (12.5%); 9 patients (7.5%) had proximal vein thrombosis and 6 (5%) had distal vein thrombosis. One patient with proximal DVT also had distal thrombosis. Bilateral DVT occurred in one patient and five of the unilateral DVT's were on the non-operative side.

Of the 108 patients in the unfractionated heparin group, DVT was detected in 27 patients (25%); 20 (18.5%) had proximal vein thrombosis and seven patients (6%) had distal vein thrombosis. Five patients with proximal DVT also had distal thrombi. There were three bilateral venous thrombi and five of the thrombi occurred on the non-operative side.

The incidence of total and proximal DVT were significantly lower in the enoxaparin group, than in the unfractionated heparin group, p = 0.03 and p = 0.014 respectively.

Of the patients in the unfractionated heparin group with cemented prosthesis, fifteen developed proximal vein thrombosis and seven distal vein thrombosis compared to six proximal and five distal thrombi in patients with cemented prosthesis in the enoxaparin group. Conversely there were five proximal thrombi in patients in the unfractionated heparin group with non cemented arthroplasties compared to three proximal and one distal thrombi in the patients in the enoxaparin group.

The incidence of proximal or distal DVT was not significantly different in patients receiving cemented or non-cemented prostheses.

Bleeding Complications

Two patients had major bleeding complications and three patients had minor bleeding complications (Table 3). The two patients with major bleeding were in the enoxaparin group. One patient developed a wound hematoma postoperatively. This patient had a prolonged APTT which was 17 seconds longer than control prior to surgery and hence was randomized in error. The second patient developed melena and was found to have duodenal ulcers by endoscopy.

Of the three patients with minor bleeding complications, one was in the enoxaparin group, and the other two in the unfractionated heparin group. The patient with minor bleeding who received enoxaparin had epistaxis on day 6. The minor bleeding complications in the unfractionated heparin group were hematuria and rectal bleeding.

Red cell transfusion requirements were comparable perioperatively in both groups, but were significantly higher post operatively in the unfractionated heparin group (1.09 ± 1.63) compared to the enoxaparin group (0.66 ± 1.11), p = 0.035. The total red cell transfusion requirements were also significantly higher in the unfractionated heparin group (3.84 ± 1.70) versus (3.37 ± 1.8), p = 0.039 (irregular distribution; Kruskan's test).

The lowest hemoglobin levels were seen on the third or fourth postoperative day for both treatment groups. At that time, the hemoglobin level was significantly higher in the enoxaparin group (12.524 ± 1.693), than in the unfractionated heparin group (11.993 ± 2.150), p = 0.002.

Anti-Factor Xa Levels

In the enoxaparin group, the anti-factor Xa levels rose to 1.5 μg/ml at day 1 and remained at approximately that level up until the last day of treatment. In the heparin group, the anti-factor Xa level remained low between 0.5 and 0.8 μg/ml throughout.

Table 2 Incidence of deep vein thrombosis

		Enoxaparin	Heparin	Total	p
Phlebography performed		120	108	228	
Mean number of days postop. ± sd		12.1 ± 1.7	11.7 ± 2.0		0.18
Number of patients with DVT	distal	6 (5%)	7 (6%)		
	proximal	9 (7.5%)	20 (18.5%)		p = 0.014
	total	15 (12.5%)	27 (25%)		p = 0.03

Table 3 Bleeding complications and blood loss in the two study groups

	Enoxaparin	Heparin
Bleedings No. of patients		
Major	2	0
Minor	1	2
Hemoglobin g/100 ml (mean ± sd)		
Before surgery	13.423 ± 1.269	13.256 ± 1.110
Day 1	13.398 ± 1.437	13.120 ± 1.794
Day 3, 4	12.524 ± 1.693	11.993 ± 2.150
Day 10	12.164 ± 1.273	12.319 ± 1.363
Transfusions – red cells units (mean ± sd)		
Perioperatively	2.69 ± 1.14	2.76 ± 0.75
Postoperatively	0.664 ± 1.118	1.091 ± 1.634
Total transfusions	3.37 ± 1.81	3.84 ± 1.70

Death and Pulmonary Embolism

There were no deaths. Five patients developed symptoms of pulmonary embolism two in the enoxaparin group, and three in the heparin group. Only one PE which was in a patient who received unfractionated heparin was confirmed by angiography.

Discussion

In patients undergoing elective hip surgery the incidence of postoperative deep vein thrombosis is approximatively 50% if prophylaxis is not used. Between 20–30% of such thrombi occur in proximal veins, and the frequency of fatal pulmonary embolism is between 1–5% (15, 16). Enoxaparin has been reported to reduce the frequency of thrombosis from 48 to 11% in a placebo-controlled randomized trial of patients having elective hip surgery (1). Although a number of studies have reported that unfractionated heparin reduces the incidence of postoperative venous thrombosis (4–9), it is not widely used because of concern for bleeding and controversy on its effectiveness.

In our double-blind randomized study we compared once-daily enoxaparin with three-times daily unfractionated heparin. Thrombosis was assessed by performing a phlebography routinely on days 12–14 or earlier if patients developed symptoms of thrombosis. The incidence of thrombosis was significantly lower in the enoxaparin group than in the unfractionated heparin group. This difference was evident for all thrombi and for proximal thrombi. The rates of bleeding and wound hematoma were low in both groups and were not statistically significantly different. However, the fall in Hb and red cell transfusion requirements were statistically significantly greater in the unfractionated heparin group.

Given that the observed rates of clinically important bleeding were low in both groups and that no difference was detected, it is likely that studies of much larger patient numbers would be required to detect differences in hemorragic events between patients who received unfractionated heparin compared to low

molecular weight heparin. Nonetheless the difference in transfusion requirements and daily hemoglobin levels between groups in our study, suggests that enoxaparin, low molecular weight heparin, is less hemorrhagic than standard unfractionated heparin when used as prophylaxis in patients undergoing elective hip surgery.

The incidence of thrombosis observed with enoxaparin compares favourably with the results of prophylaxis with pre/post-operative oral anticoagulant therapy (17, 18) and with adjusted dose heparin (19). Low molecular weight heparin has advantages over these methods of prophylaxis since it appears that it can be given in a fixed dose and without laboratory monitoring. Although, the incidence of thrombosis in the enoxaparin group, in our study, was similar to that reported by Turpie et al. (1), the dosage regimens used in these two studies were different. Turpie commenced prophylaxis post-operatively and used a dose of 30 mg twice daily, while in our study enoxaparin was commenced preoperatively and was administered as a once-daily dose of 40 mg. We elected to use a once-daily dose of enoxaparin because pharmakokinetic studies (20–24) and other clinical trials (2, 3) suggested that it would be effective when administered in this way. In addition our results did not confirm a previous study (25) which observed a lower incidence of DVT in patients receiving a non cemented prosthesis.

Finally our study supports the results of experimental and clinical studies with low molecular weight heparin indicating that enoxaparin is an effective antithrombotic agent in a group of patients at high risk for both thrombosis and bleeding.

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