A Comparative, Double-blind, Randomised Trial of a New Second Generation LMWH (Bemiparin) and UFH in the Prevention of Post-operative Venous Thromboembolism

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Key words
Heparin, prevention of venous thromboembolism

Summary

A randomised, prospective, double-blind trial was performed, to compare the safety and efficacy of a new low-molecular-weight heparin (LMWH) Bemiparin and standard unfractionated heparin (UFH), for the prophylaxis of postoperative venous thromboembolism. 300 patients scheduled to undergo elective hip arthroplasty were included. The principal outcome measures were the incidence of thromboembolic events and bleeding complications. 149 patients received 3,500 anti-Xa IU of bemiparin plus a placebo injection daily and 149 patients received 5,000 IU of UFH twice a day.

The two groups were similar with respect to factors likely to affect the risk of developing post-operative venous thromboembolism (VTE) and risk of bleeding events. During the post-operative period, 34 patients developed VTE complications; 9 (7.2%) in the bemiparin group and 25 (18.7%) in the UFH group. VTE in the two groups was statistically significant (OR of 2.96; 95% CI 1.32-6.62 and p = 0.01).

There were no significant differences in the frequency of bleeding complications: major bleeding requiring discontinuation of prophylaxis, (OR 1.21; 95% CI 0.36-4.05; p = 1.00), the measured median operative blood loss (p = 0.77) or the median postoperative drain loss (p = 0.97), and the number of patients who developed wound haematoma (OR 0.87; 95% CI 0.31-2.46; p = 1.00).

A comparison of coagulation parameters on the preoperative day with post-operative day 2 ± 1, day 6 ± 1 and day of discharge showed a significantly higher AT concentration, anti-factor Xa activity and TFPI levels in the bemiparin group when compared with UFH.

This study demonstrates that bemiparin, in a single daily subcutaneous dose of 3,500 anti-Xa IU in high risk patients undergoing hip arthroplasty is more effective than UFH administered twice daily at a dose of 5,000 IU in the prevention of postoperative VTE. Both agents are equally safe.

Introduction

Hip surgery, whether elective or performed as an emergency, is associated with a high incidence of thromboembolic complications. In a recent metaanalysis of controlled clinical studies, the average documented incidence of lower limb deep vein thrombosis was 46% among the placebo-treated patients (1). Almost 50% of these thrombi localised above the knee; a site which is associated with a risk of pulmonary embolism and were thus deemed to be clinically important. The high incidence of proximal vein thrombosis is thought to be the result of the intraoperative manipulation of the leg, causing local vascular wall damage with subsequent activation of coagulation. According to Virchow’s triad, postoperative stasis is another important risk factor provoking this high incidence.

The use of low dose heparin, given subcutaneously has been the most promising approach for preventing venous thromboembolism to date. Adoption of this technique had led to 50% decrease in the incidence of deep vein thrombosis and 75% reduction in the risk of developing fatal pulmonary embolism. However, this approach had two major disadvantages, firstly, heparin had to be administered at an interval of 8 to 12 hours and secondly, there is a definite increased risk of bleeding, mostly in the form of wound haematoma (2). Low molecular weight heparins (LMWHs) represent the most significant recent development in prophylaxis against VTE (3). The potential advantages for their use as prophylactic antithrombotic agents include a two-to-four fold longer plasma half-life when compared to commercially available unfractionated heparin (UFH) at therapeutic doses, and 90-95% bioavailability following subcutaneous administration, thus enabling a single daily dosing (3). Furthermore, for an equivalent antithrombotic effect, they are less likely to cause haemorrhage, especially in surgical patients during the perioperative period (4). Currently, preparations of LMWH in general use are prepared by different techniques, have a variable molecular weight distribution and therefore are likely to have different pharmacokinetic properties. A greater understanding of structure activity relationships (5) has led to further modifications in manufacturing process, resulting in a second generation LMWH with a lower mean molecular weight and a more precisely defined composition of polysaccharide chains. Bemiparin represents such a LMWH which may have a better efficacy profile and reduced risk of haemorrhage when compared to UFH. To test this hypothesis, a double blind, randomised trial was performed in high risk patients undergoing total hip arthroplasty and the results are reported in this paper.
Methods

The study was multicentre, prospective, randomised and double-blind with three Institutions participating. The study protocol and informed consent forms were approved by each centre's ethics committee and performed in compliance with the revised declaration of Helsinki and Good Clinical Practice guidelines (GCP).

Patients

Men and women aged 40 years or more, scheduled for elective hip replacement with an expected hospital stay of at least 12 ± 4 postoperative days and consenting to participate in the study were included.

Exclusion criteria were congenital or acquired haemorrhagic diathesis, known thrombocytopenia (platelet count < 80,000/mm³), hypertension (SBP > 200 mmHg, DBP > 100 mmHg) active gastrointestinal ulcer or active malignant disease, impaired renal function (serum urea > 120 mg/L or creatinine > 2.0 mg/L), allergy to heparin, or iodine containing radio-opaque contrast media, hyperthyroidism, pregnant women or those breast feeding for less than 6 months post partum or of childbearing potential, and patients already receiving anticoagulants.

Study Medication

Bemiparin administered in this trial, was prepared by a novel method of depolymerisation and then subjected to fractionation to prepare a compound of precise molecular weight. The average molecular weight is 3,600 daltons and, as such, it is considered to be one of the second generation low molecular weight heparins. A comparison of the anticoagulant properties of bemiparin with that of UFH showed that it has a specific anti-Xa activity of 90 IU/mg and anti-factor IIa of 10 IU/mg. The specific activity of UFH is 160 IU/mg in both assays.

Eligible patients were randomly allocated to receive subcutaneous injections of either 3,500 IU of bemiparin once daily plus a placebo injection containing sterile 0.9% saline or 5,000 IU UFH twice daily. Prefilled syringes, prepared by Laboratorios FARMACEUTICOS Rovi, S.A. were identical in appearance. Boxes were labelled with the trial code number and contained 32 prefilled syringes, sufficient for 12 ± 4 days of therapy. Syringes containing morning and evening doses were clearly labelled and the pre-operative dose was also labelled. Injections were given subcutaneously in the anterior abdominal wall and a nurse signed the drug chart after each injection. Prophylaxis began 2 hrs before surgery: it was continued for at least 8 post-operative days or longer if the patient was still institutionalised.

Study Design

The study sample size was calculated on an assumed incidence of deep vein thrombosis of 25% in the group receiving 5,000 IU of UFH twice daily which would be reduced to 10% in those receiving 3,500 IU of bemiparin per day. Two hundred and twenty four evaluable patients would be required with equal numbers in each group, to give a 90% probability of detecting a difference at two sided 5% level of confidence with α = 0.05 and β = 0.02. The sample size was increased to 300 to allow for patient drop outs in whom there may be incomplete assessment or those who did not undergo adequate venography.

The comparison between treatment arms were performed using Student t-test for continuous variables and a chi-square test with Yates correction (or Fisher’s exact test when appropriate) for categorical variables. The odds ratio (OR) and 95% confidence intervals (CI) were computed for primary binary outcomes. Paired student t-test was used for within group comparisons of continuous variables. Two sided significance levels were computed.

Assessment

The primary determinant of efficacy was the incidence of deep vein thrombosis determined by bilateral elective venography performed on postoperative day 12 ± 4. All venograms were assessed “blindly” by an independent expert radiologist, commenting on the site and extent of thrombi. Thrombi were considered to be present when an intraluminal filling defect seen on at least two radiographs remained constant in shape and location. Pulmonary emboli suspected on clinical symptoms were confirmed by ventilation perfusion lung scanning. The treatment for either DVT and/or PE was recorded.

Pulmonary embolism was considered to have been fatal if necropsy revealed massive fresh emboli in the pulmonary trunk, main pulmonary artery or in at least two lobar arteries where no other cause of death was found.

Determinants of safety were the incidence of major or minor bleeding episodes. Excessive blood loss during surgery was subjectively assessed by the surgeon. All postoperative drain losses and the amounts of transfusion given were recorded as were the following postoperative bleeding complications: wound haematoma, bleeding leading to withdrawal of prophylaxis, reoperation to control bleeding or to evacuate wound haematoma.

Serious Adverse Events

All serious and nonserious adverse events observed during the prophylactic period were recorded. Serious adverse events included death, life threatening events and events that resulted in prolonged hospitalisation.

Laboratory Parameters

The laboratory parameters were determined before surgery (day –1) and on postoperative day 2 ± 1 and 6 ± 1 as well as on the day of discharge (day 12 ± 4). Blood samples were withdrawn 2-4 h after the first daily heparin injection. Samples were processed and analysed at a central laboratory.

Activated partial thromboplastin time (aPTT) (6), antithrombin (AT) concentration (7), anti-factor Xa activity and TFPI activity (8) were measured by using routine laboratory techniques. For aPTT measurements, bovine cephalin used was supplied by Instrumentation Laboratory (UK). For TFPI activity measurement, substrate S2765 was supplied by Quadracletech company (UK), Factor VIIa and Factor Xa by Enzyme Research Laboratory (UK) and Tissue Thromboplast, Sigma Diagnostic (UK). The haematological profiles included haemoglobin, haematocrit and erythrocyte, leucocyte and platelet counts. Biochemical parameters assessed included serum electrolytes and liver function tests.

Results

300 patients were entered into the trial; in two patients planned operation was postponed and they were therefore excluded from analysis of results. The remaining 298 patients were randomised into two groups; 149 patients received LMWH and 149 UFH. An intention-to-treat analysis for safety and per protocol analysis for efficacy was undertaken.

Baseline Characteristics and Risk Factors

The two groups were similar with respect to sex, age, bodymass index, and other risk factors that alter the risk of postoperative VTE (Table 1), and the type of prosthesis used, duration of surgery and type of anaesthesia given (Table 2). The distribution of other risk factors which could be associated with a high frequency of bleeding events were also similar in two groups. The number of patients using analgesics including Aspirin was 84 (56.4%) in the bemiparin group and 88 (59.1%) in the UFH group, other nonsteroidal antiinflammatory drugs (NSAID’s) were used by 56 (37.6%) and 56 (37.6%) respectively.

Mortality

One patient in the bemiparin group died on the third postoperative day, following gastric haemorrhage which was confirmed to be the
cause of death at autopsy. Three other patients, 2 in the bemiparin group and one in the UFH group died during the follow-up period. Details of these are provided in the section – Follow up results.

**Comparison of Safety Parameters**

Two hundred and ninety eight patients received at least one dose of study drug and were included in the analysis of safety. The results are presented in Table 3. Major bleeding which required discontinuation of prophylaxis occurred in 5 patients (3.4%) receiving bemiparin and 6 (4.0%) receiving UFH; the difference is not significant (OR of 1.21; 95% CI 0.36-4.05, p = 1.00). The measured median operative blood loss in the bemiparin group was 500 ml and 610 ml in the UFH group (p = 0.77). 74 (49.7%) of patients in the bemiparin group and 66 (44.3%) in the UFH group received blood transfusions (p = 0.42). Blood loss was also analysed in relationship to general or epidural/spinal anaesthesia. In the bemiparin group, the median operative loss was 400 ml in epidural/spinal compared to 613 ml in those receiving general anaesthesia (p = 0.007). Similarly, in the UFH group, median loss was 400 ml and 700 ml respectively (p = 0.006).

In the bemiparin group, 8 patients (5.4%) and 7 (4.7%) in the UFH group developed wound haematoma (OR 0.87, 95% CI 0.31-2.46; p = 1.00). None of these patients required reoperation either to control bleeding or evacuate wound haematoma.

**Comparison of Efficacy**

The efficacy assessment was based on the frequency of venous thromboembolism (VTE). Thirty nine patients were discharged before the 8th postoperative day and were considered protocol violators. Therefore, 259 patients were included in the efficacy analysis. Three patients developed clinical features of PE which were confirmed by VQ lung scanning; 1 (0.8%) of these had received bemiparin and 2 (1.5%) UFH (OR 1.88; 95% CI 0.18-21.00, p = 0.03). Location of thrombi detected in the two groups is presented in Table 4. 34 patients (13.1%) developed VTE complications, 9 (7.2%) in the heparin group and 25 (18.7%) in the UFH group. The difference in frequency of total VTE venography had not been performed due to patients refusal, technically unfeasible (investigator’s decision) or venograms could not be evaluated. Of 217 patients who had evaluable venograms, 101 patients received bemiparin and 116 received UFH. DVT was detected in 33 patients, 9 (8.9%) in the bemiparin group and 24 (20.7%) in the UFH group (OR 2.67; 95% CI 1.18-6.05, p = 0.03). Location of thrombi detected in the two groups is presented in Table 4. 34 patients (13.1%) developed VTE complications, 9 (7.2%) in the heparin group and 25 (18.7%) in the UFH group. The difference in frequency of total VTE

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**Table 1** Demographic data

<table>
<thead>
<tr>
<th></th>
<th>BEMIPARIN (n = 149)</th>
<th>UFH (n = 149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (± SD)</td>
<td>70.4 ± 10.9</td>
<td>70.5 ± 9.2</td>
<td>0.92</td>
</tr>
<tr>
<td>BMI Mean (± SD)</td>
<td>25.3 ± 4.1</td>
<td>25.6 ± 4.6</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**Table 2** Operative and anaesthetic details

<table>
<thead>
<tr>
<th></th>
<th>BEMIPARIN (n = 149)</th>
<th>UFH (n = 149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Details:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (mins.)</td>
<td>110 ± 55.1</td>
<td>109.9 ± 58.7</td>
<td>0.207</td>
</tr>
<tr>
<td>Cemented</td>
<td>133 (90.5%)</td>
<td>143 (96.6%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Cementless</td>
<td>8 (5.4%)</td>
<td>1 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Hybrid</td>
<td>4 (2.7%)</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.3%)</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Assessment of safety variables

<table>
<thead>
<tr>
<th></th>
<th>BEMIPARIN (n = 149)</th>
<th>UFH (n = 149)</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis discontinued</td>
<td>5 (3.4%)</td>
<td>6 (4.0%)</td>
<td>1.21</td>
<td>0.36 - 4.05</td>
<td>1.00</td>
</tr>
<tr>
<td>Operative blood loss (median)</td>
<td>500.0</td>
<td>610.0</td>
<td></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>PO Drain loss (median)</td>
<td>350.0</td>
<td>380.0</td>
<td></td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Patient transfused</td>
<td>74 (49.7%)</td>
<td>66 (44.3%)</td>
<td>0.81</td>
<td>0.51 - 1.27</td>
<td>0.42</td>
</tr>
<tr>
<td>Wound haematoma</td>
<td>8 (5.4%)</td>
<td>7 (4.7%)</td>
<td>0.87</td>
<td>0.31 - 2.46</td>
<td>1.00</td>
</tr>
</tbody>
</table>
between the two groups were also statistically significant with 9 patients (7.2%) in the bemiparin group and 25 in the UFH group (OR 2.96; 95% CI 1.32-6.62; p = 0.01).

**Laboratory Parameters**

Laboratory parameters were measured before surgery; on postoperative days 2 ± 1, 6 ± 1 and on the day of discharge. Among haematological parameters including haemoglobin, haematocrit, erythrocyte, leucocyte and platelet count, there were no significant differences between patients receiving either bemiparin or UFH. Biochemical parameters assessed included serum electrolytes, total protein, albumin, bilirubin, alkaline phosphate and transaminases (ALT, AST) and Gamma GT to determine if there was any cumulative adverse effect on hepatic or renal function. No significant differences were observed in values for any of these parameters in comparison with preoperative or postoperative values including day of discharge (data not shown).

Preoperative assessment of coagulation parameters including aPTT, AT, anti-Factor Xa and TFPI activity showed no significant difference between the two treatment groups (Table 5). On the postoperative day 2 ± 1, the median anti-Xa activity of 0.3 IU/ml was significantly higher in the bemiparin group, compared with 0.0 IU/ml in the UFH group, (p = 0.001). TFPI activity levels were also found to be significantly higher in the bemiparin group at 165% compared to 151% in the UFH group, (p = 0.017). On the post-operative day 6 ± 1, significantly higher levels were again observed in patients receiving bemiparin for AT concentration (p = 0.002), anti-Xa levels (p <0.001) and aPTT (p = 0.014). Samples withdrawn on the day of discharge from patients receiving bemiparin again showed significantly higher AT concentration (p = 0.048) and anti-Xa levels (p <0.001). In addition, the median TFPI level of 198% in the bemiparin group was higher than 176% in the UFH group (p = 0.009).

**Follow-up after Discharge from Hospital**

Although the study design required a late follow-up evaluation, approximately 4 weeks after day of discharge and occurrence of DVT and/or pulmonary embolism in this period were to be documented, the period was extended in order to assess the full impact of adverse events which occurred during post discharge from hospital. Three patients died during the follow-up period; 2 had received bemiparin and 1 UFH. One patient who had received bemiparin developed a DVT in the left limb – which required prolonged hospitalisation, and also developed a hip dislocation, one month later which required reoperation. This patient ultimately died on the 54th day due to myocardial infarction, confirmed at autopsy. A second patient who was discharged home on the 11th post-op day, died due to a massive PE, confirmed by autopsy on the 21st post-op day. The third patient had received UFH and elective venography on the 8th post-op day showed left tibial vein isolated thrombosis, which was not treated with therapeutic doses of heparin. He died on the 19th post-op day at home, autopsy confirmed the cause of death as massive pulmonary embolism.

Another 3 patients who had received UFH developed non-fatal PE and/or DVT during the follow-up period. The diagnosis of PE was confirmed by a mis-match in the perfusion-ventilation lung scan in one. The second patient was admitted with clinical suspicion of PE which was not confirmed by lung scanning. The third patient developed DVT confirmed by phlebography. They made a complete recovery following I.V. heparinisation and oral anticoagulant therapy.

**Adverse Events**

Thirty seven patients suffered adverse events either during in-patient stay or during the follow-up period. Of these, 22 (17.6%) patients had received bemiparin, compared to 15 (11.2%) receiving UFH; the difference in frequency is not statistically significant (OR 0.59; 95% CI 0.27-1.26; p = 0.20). The protocol required a hospital stay of 12 ± 4 days after surgery. Therefore, patients who required prolonged hospitalization due to any reason were deemed to have suffered from an adverse event. Hospital stay was prolonged in 16 patients – 10 received bemiparin and 6 UFH. Six patients in the bemiparin group and 3 in the UFH group were readmitted for further treatment.

### Table 4  Assessment of efficacy variables – details of DVT

<table>
<thead>
<tr>
<th></th>
<th>BEMIPARIN (n = 125)</th>
<th>UFH (n = 134)</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>9 (7.2%)</td>
<td>25 (18.7%)</td>
<td>2.96</td>
<td>1.32-6.62</td>
<td>0.01</td>
</tr>
<tr>
<td>PE</td>
<td>1 (0.8%)</td>
<td>2 (1.5%)</td>
<td>1.88</td>
<td>0.17-21.00</td>
<td>1.00</td>
</tr>
<tr>
<td>DVT</td>
<td>9 (9.9%)</td>
<td>24 (20.7%)</td>
<td>2.67</td>
<td>1.18-6.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Proximal</td>
<td>3 (3.0%)</td>
<td>5 (4.3%)</td>
<td>1.47</td>
<td>0.34-6.32</td>
<td>0.73</td>
</tr>
<tr>
<td>Distal</td>
<td>4 (4.0%)</td>
<td>13 (11.2%)</td>
<td>3.06</td>
<td>0.37-9.71</td>
<td>0.08</td>
</tr>
<tr>
<td>Proximal &amp; Distal</td>
<td>2 (2.0%)</td>
<td>6 (5.2%)</td>
<td>2.7</td>
<td>0.53-13.69</td>
<td>0.23</td>
</tr>
</tbody>
</table>

### Table 5  Median changes in coagulation parameters

<table>
<thead>
<tr>
<th></th>
<th>BEMIPARIN</th>
<th>UFH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-factor Xa (IU/ml)</td>
<td>Pre-operative</td>
<td>0.0 (0.1)</td>
<td>0.0 (0.1)</td>
</tr>
<tr>
<td>day 2±1</td>
<td>0.3 (0.2)</td>
<td>0.0 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>day 6±1</td>
<td>0.3 (0.1)</td>
<td>0.0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>discharge day</td>
<td>0.3 (0.2)</td>
<td>0.0 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AT (%baseline)</td>
<td>Pre-operative</td>
<td>108 (24.5)</td>
<td>109 (30.0)</td>
</tr>
<tr>
<td>day 2±1</td>
<td>97.0 (26.0)</td>
<td>95.0 (26.0)</td>
<td>0.617</td>
</tr>
<tr>
<td>day 6±1</td>
<td>112 (30.0)</td>
<td>101 (26.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>discharge day</td>
<td>112 (26.2)</td>
<td>105 (25.6)</td>
<td>0.048</td>
</tr>
<tr>
<td>aPTT ratio</td>
<td>Pre-operative</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>day 2±1</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.3)</td>
<td>0.042</td>
</tr>
<tr>
<td>day 6±1</td>
<td>1.3 (0.5)</td>
<td>1.2 (0.3)</td>
<td>0.014</td>
</tr>
<tr>
<td>discharge day</td>
<td>1.2 (0.3)</td>
<td>1.1 (0.5)</td>
<td>0.074</td>
</tr>
<tr>
<td>TFPI (% control)</td>
<td>Pre-operative</td>
<td>158 (69.1)</td>
<td>154 (65.9)</td>
</tr>
<tr>
<td>day 2±1</td>
<td>165 (68.6)</td>
<td>151 (55.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>day 6±1</td>
<td>191 (67.1)</td>
<td>177 (55.8)</td>
<td>0.064</td>
</tr>
<tr>
<td>discharge day</td>
<td>196 (67.5)</td>
<td>170 (58.3)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Abbreviations and symbols:  
aPTT = activated partial thromboplastin time  
AT = antithrombin III  
TFPI = tissue factor pathway inhibitor  

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Discussion

The objective of this prospective, double-blind, randomly allocated trial was to compare the safety and efficacy of a new LMWH (bemiparin) and UFH for perioperative thromboprophylaxis in patients undergoing elective hip arthroplasty. The study was designed on the assumption of an expected incidence of DVT of 25% in the UFH group, reduced to 10% in the bemiparin group. The results showed that 7.2% of patients receiving bemiparin and 18.7% receiving UFH developed post-operative VTE. The difference is statistically significant, OR 2.96; 95% CI 1.32-6.62, and p = 0.01. It is possible that these differences in the frequency of VTE in the two groups could have been due to other factors than LMWH, likely to influence postoperative DVT (9).

Although the history of a previous episode of DVT or PE was higher in UFH group, the difference was not significant for either (p = 0.07 and p = 0.61 respectively). The distribution of other risk factors including obesity, varicose veins, type and duration of surgery and anaesthesia, showed no significant difference between the two groups. It can be assumed that a single daily injection of 3,500 anti-factor Xa IU of bemiparin is more effective in preventing post-operative VTE after hip arthroplasty than 10,000 IU of UFH.

One of the issues which is currently being discussed is the greater safety of LMWHs. The second aim of this trial was to compare the safety of two heparins. No significant differences were observed in excessive operative or post-operative drain loss, frequency of wound haematoma (OR 0.87; 95% CI 0.31-2.46; p = 1.00) or major bleeding requiring discontinuation of prophylaxis or reoperation to control it. A recent study has suggested that patients who have excessive perioperative bleeding while receiving heparin prophylaxis are usually older, more likely to be male, or to be taking NSAIDs (10). Once again, the analysis of the demographical data and concomitant medication showed no significant difference between the two groups. Therefore, it is likely that similar frequency of perioperative bleeding observed in the present study indicates equivalence in their safety profiles.

Assessment of laboratory parameters of haemostasis revealed significant differences between the two groups. While the preoperative assessment of patients receiving either heparin with regard to aPTT, AT, anti-Factor Xa and TFPI activity levels showed no significant difference, significantly higher mean anti-Xa levels were observed in the patients receiving bemiparin on postoperative days 2, 6 and on day of discharge. Significantly higher levels of AT concentration, aPTT and TFPI activity were also observed in the patients receiving bemiparin. The clinical importance of these changes needs to be investigated in greater detail before definitive conclusions can be reached. It has been suggested that measurement of anti-Xa levels may be of help in assessing the likelihood of developing thrombosis (11-12), although this finding is not consistent (13). It is likely that the low incidence of DVT observed in patients receiving bemiparin is related to a persistently higher anti-Xa activity. Furthermore, higher levels of AT concentration and the TFPI activity observed in the patients receiving bemiparin may also contribute to its superior anti-thrombotic efficacy. Very high concentrations of tissue factor (TF) exist in the bone marrow and TF is released into the circulation during the reaming of the acetabulum and femoral shaft (14). The release of TF is accompanied by a 200-fold increase in systemic circulating fibrinopeptide A during surgery and 5-fold increase in thrombin-antithrombin complexes up to 4 weeks after operation, both markers representing increased thrombin generation (15). Furthermore, crushed adipose tissue derived from fractured bone also contains a very high concentration of TF. Higher levels of AT concentration and the TFPI activity observed in the patients receiving bemiparin as compared to UFH may also contribute to its superior anti-thrombotic efficacy.

This study may be criticised on two counts, one relating to the regimen of UFH used and the second the time of initiation of prophylaxis. Currently, two regimens of UFH 5,000 IU either 8 hourly or 12 hourly are used to protect patients undergoing hip arthroplasty against thrombosis. It could be argued that a more appropriate comparison with bemiparin should have included an 8 hourly UFH regimen. However, a meta-analysis analysed the data of the trials, where the frequency of treatment was either 8 or 12 hourly (16). There was no difference in the efficacy of different regimens with a 72 percent reduction in VTE for the 8 h regimen and a 68 percent reduction for the 12 h regimen. This remained true even when the analysis was confined to patients at a high risk of thrombosis, such as those in the orthopaedic surgery trials (68 ± 10 percent reduction for the 8 or 12 hourly regimen). The risk of bleeding also did not appear to depend on the frequency of treatment (increased risk of 66 ± 14 percent in the 8 hour group and 65 ± 18 percent in the 12h group) (16).

Although both the preoperative and postoperative initiation of prophylaxis for DVT/PE with LMWH is advocated, the relative effectiveness and safety of these approaches is not known. The results of a recent meta-analysis of randomised level I trials showed that prophylaxis with LMWH initiated pre-operatively was associated with a DVT frequency of 10% compared with a frequency of 15.3% when the LMWH was initiated postoperatively (p = 0.02 Fisher exact test) (17). Furthermore, major bleeding was less frequent in patients receiving preoperatively initiated LMWH than in patients receiving post-operatively initiated LMWH (0.9% vs. 3.5%; p = 0.01 Fisher exact test). Thus, preoperative initiation of prophylaxis used in this study appears appropriate.

In the current trial, none of 72 patients having spinal or epidural anaesthesia developed neurological complications. Recently, concern has been expressed about the development of spinal or epidural haematomas when anticoagulants are administered concurrently (18, 19). Neurological dysfunction due to bleeding after neuraxial blockade is very rare with an estimated incidence of less than 0.5 per 100,000 for spinal anaesthetics and 0.7 per 100,000 epidural anaesthetics (20). From extensive experience in Europe where traditionally, prophylaxis is given 12 hrs before surgery, there is little evidence that preoperative administration of low dose UFH or LMWH increases the risk of spinal haematoma after regional anaesthesia (21, 22, 23). However, the experience in the United States is different (24). Several factors may account for this difference, the most important being the different dosage of LMWH where enoxaparin in a dose of 30 mg (3000 U) twice daily is used in the United States and 40 mg (4000 U) once daily in Europe. The twice-daily dose although providing a greater degree of anticoagulation may affect the safe placement and removal of spinal and epidural needles and catheters (24). It is now recommended that epidural catheters be removed at least 12 hrs after the last injection of LMWH or immediately (1-2 hrs) prior to the next dose (24).

Endothelial injury in veins draining the operative area (26), enhanced local and systemic activation of coagulation, and depressed fibrinolytic activity are responsible for initiation of thrombi during surgery and their subsequent growth in the immediate postoperative period (27). Late venous thromboembolism after discharge from hospital, when prophylaxis has been discontinued, occurs in a further 10.5% of patients undergoing hip operations. Four recent studies have confirmed this incidence of late VTE. The efficacy and safety of LMWHs administered for either one or five weeks has been established (28-31). The results indicate that the frequency of DVT 28-35 days after operation in the placebo group who did not receive prolonged thrombo-
prophylaxis varied between 11.8-39.0%, whereas in those receiving prolonged prophylaxis it was 4.4-18%. Although the absolute rate of phlebographically verified DVT differed in these four studies, the relative reductions in the treatment groups were comparable (RR 0.39-0.63). Taking the data of all the studies together, it can be argued that prolonged prophylaxis with self-administered LMWH following discharge from hospital is more effective than a standard 7-10 day regimen confined of in-patient prophylaxis. In the present study, follow-up evaluation was extended to 56 days after operation. Only one out of 149 patients who had received bemiparin died of PE on the 21st post operative, confirmed by autopsy. In contrast, 4 of the 149 patients who had received UFH suffered a post-discharge venous thromboembolic event, one of these being a fatal PE on the 19th post-operative day. These data suggest that bemiparin, which we have demonstrated to be more effective than UFH in controlling the activation of coagulation during the in-patient stay, may provide continued protection in the early post-discharge period. However, this issue can only be resolved in a prospective study designed to address this specific question.

LMWHs may have different and more favourable pharmacokinetic properties than UFH because of their higher content of BCLM (Below Critical Length Material MW <5,400 daltons) (5). BCLM has a significantly longer biological half life and is responsible for the anti-Xa activity. In comparison, ACLM (Above Critical Length Material MW >5,400 daltons), mediates both the anti-IIa and anti-Xa activities of heparin. When administered subcutaneously, a greater proportion of BCLM material is absorbed than ACLM. Bemiparin represents a second generation LMWH, because it has a mean molecular weight of 3,600 daltons, more than 80% of polysaccharide chains within the range of 2,000-8,500 daltons. Therefore, it is likely that a high proportion of BCLM material is present within this well-defined molecular weight range and this contributes to its superior anti-thrombotic activity.

In conclusion, this prospective randomised double blind trial has demonstrated that bemiparin, a second generation LMWH, administered subcutaneously once daily, at a dose of 3,500 IU in high risk patients undergoing hip arthroplasty is more effective but equally safe in preventing post-operative DVT than standard UFH administered twice daily at a dose of 5,000 IU.

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APPENDIX

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