Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery†

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Summary
The benefit/risk ratio of administering heparin during spinal anaesthesia in patients undergoing total hip replacement (THR) has not been studied widely. We conducted a prospective, randomized, double-blind study to compare low molecular weight heparin (LMWH) for 10 days and placebo in patients undergoing THR performed under spinal anaesthesia associated with gradual compression stockings. Efficacy was assessed by systematic bilateral ascending venography on day 10 in a sequential analysis. Among the 170 patients enrolled, data were available in 153 patients. In the LMWH group (n=78) the total incidence of deep vein thrombosis (DVT) was 14.1% compared with 37.3% in the placebo group (n=75) (P=0.0016). No gross neurological sequelae were observed during the study. This study showed that the addition of LMWH in patients undergoing THR under spinal anaesthesia and wearing gradual compression stockings significantly decreased the incidence of venogram-proved DVT. (Br. J. Anaesth. 1997; 78: 660–665).

Key words

It is well recognized that patients undergoing total hip replacement surgery (THR) are at high risk of developing venous thromboembolism. Fatal pulmonary embolism may occur in 1–5% of these patients.1–3 Without thromboprophylaxis, incidences of venogram-proved deep vein thrombosis (DVT) of up to 50% have been reported.4 Several clinical studies have demonstrated the effectiveness and high benefit/risk ratio of low molecular weight heparins (LMWH) in the prophylaxis of DVT,4–7 and meta-analyses have confirmed their role in patients undergoing orthopaedic surgery.8 9 Central neural block (extradural anaesthesia or subarachnoid anaesthesia) is used widely in orthopaedic surgery. Spinal anaesthesia has been shown in fracture and elective hip surgery to moderately reduce postoperative DVT.10 Winter-Christensen and colleagues11 showed in 55 THR patients that extradural anaesthesia alone was as effective in preventing DVT as unfractionated heparin in combination with extradural anaesthesia. However, the association of heparin and central neural block remains questionable because of the potential risk of spinal haematoma.12 A consensus conference, held in Europe in 1991, suggested that the benefit/risk ratio of this association should be reassessed.13 This prospective, randomized, double-blind study was therefore designed to assess the benefit/risk ratio of LMWH in addition to spinal anaesthesia and gradual compression stockings in THR surgery.

Patients and methods
We considered eligible for the study consecutive patients aged more than 18 yr, weighing 45–95 kg, undergoing primary THR surgery under regional anaesthesia (subarachnoid block and catheter removed at the end of the surgical procedure), wearing gradual compression stockings (started the day before surgery).

Exclusion criteria were: re-operation for THR, surgery under general anaesthesia, patients under nail extension before surgery, history of DVT, pulmonary embolism, or both, hepatic or renal insufficiency, lung or heart failure, ASA status more than III, haemorrhagic disorders contraindicating the use of antithrombotic drugs (active ulcerative disease, uncontrolled arterial hypertension, stroke within the previous 6 months or other known haemorrhagic disorders), occurrence of a bloody tap during spinal

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patients were considered at high risk of DVT within charge as long-term prophylaxis because these enoxaparin 40 mg) for 28 days after hospital discharge. Patienst were allocated to receive subcutaneously, once daily, for 10±2 days either LMWH or placebo. All patients underwent daily clinical evaluation and systematic bilateral ultrasonicography of the lower extremities on treatment days 3 and 6. All patients underwent systematic bilateral ascending contrast venography on day 10±2 after surgery, or earlier if indicated. Patients with negative venography on day 10±2 were then given, a once-daily dose of LMWH s.c. (open label enoxaparin 40 mg) for 28 days after hospital discharge as long-term prophylaxis because these patients were considered at high risk of DVT within the month following surgery. Those with evidence of DVT detected by the investigator on systematic venography were treated using the usual therapeutic regimens. All patients were scheduled for a 3-month post-surgery follow-up. All clinical suspicions of a thromboembolic event during this follow-up period were documented by ultrasonography or venography for DVT, and by ventilation-perfusion lung scan or angiography for pulmonary embolism.

This study was conducted in accordance with the Declaration of Helsinki, European Good Clinical Practice and French Law. The study was approved by the Ethics Committee of La Pitié-Salpêtrière Hospital, Paris, France, and written informed consent was obtained from all patients before randomization.

THERAPEUTIC REGIMENS

Eligible patients operated on under spinal anaesthesia and wearing gradual compression stockings (Ted stockings provided by Kendall) were allocated randomly to receive either LMWH or placebo, using a computer-generated randomization schedule, which was equilibrated by study centre and balanced in blocks of four patients. Patients in the LMWH group received, once daily, enoxaparin 40 mg (0.4 ml) s.c., corresponding to 4000 iu of anti-Xa, for 10±2 days. Patients in the control group received subcutaneously, once daily, a 0.4-ml injection of saline s.c. (3.6 mg of sodium chloride in 0.4 ml of infusion water) for 10±2 days.

OUTCOME MEASURES

The primary efficacy outcome was defined as the occurrence of postoperative venous thromboembolic complications (confirmed DVT or pulmonary embolism) during the 10±2 postoperative days after surgery. The primary study conclusions for efficacy were based on intent to treat analysis in patients with adequate radiographic examinations reassessed by an independent central Reading Committee for venographies, angiographies or lung scans, and if necessary by a third expert from the Data and Safety Monitoring Review Board. All venograms were evaluated by two independent radiologists who were unaware of the treatment. The venograms were considered positive when a constant intraluminal filling defect was present in at least two different positions. DVT was classified as proximal when the thrombus was in the popliteal vein or above, and as distal when the thrombus was in the calf vein. Muscle veins were also taken into account in addition to DVT for safety purposes considering the estimated risk of developing a visualized thrombus in a placebo group. All patients with proximal, distal or muscle thrombi were considered as having DVT.

The secondary efficacy and safety outcomes were defined as occurrence of clinically suspected venous thromboembolic events, major or minor haemorrhagic episodes or any other serious adverse event (including death, life-threatening events and events that resulted in prolonged hospitalization or re-hospitalization) within the 3-month follow-up.

Haemorrhage was classified as major if it was overt and associated with either a decrease in haemoglobin of 2 g dl−1 or more, a need for transfusion of 2 u. or more of packed red blood cells, if it was retroperitoneal or intracranial, or if it led to surgical reintervention or death. Haemorrhage was defined as minor if it was overt but did not meet the other criteria for major haemorrhage. Intra- and postoperative blood loss was also calculated. The potential occurrence of spinal haematoma was assessed by daily patient examination performed by an anaesthetist during hospitalization. No systematic neurological assessments were required except in cases of clinical symptoms suggesting neural compression such as sensitive or motor deficit associated with back pain. The postoperative blood loss calculation was performed by the standardized method of Toy and colleagues. Measures of wound haematoma width were recorded daily. Blood samples for measurement of haemoglobin concentration and platelet count were obtained before surgery, and on days 3, 6 and 10±2.

STATISTICAL ANALYSIS

This study was conducted as a closed sequential trial. Sample size evaluation was based on the assumption of an expected incidence of DVT of 15% for the LMWH group and 25% for the control group. Considering a type I error of 5% and type II error of 20%, it was calculated that a total number of 500 patients (250 in each group) would be needed to detect such a difference. In this study the statistical
procedure was a sequential grouped analysis using the simple triangular test procedure in which the final sample size is not fixed in advance. In this procedure, data concerning the primary efficacy endpoint were analyzed after every 50 patients. In these conditions, the maximum final sample size could be a total number of 750 patients (375 patients in each group), corresponding to a maximum number of 15 inspections. Two statistical assessments were calculated: the first was a cumulative measure of the difference between the LMWH group and the control group, the second was a measure of the information available in the study. A plot of these two statistics was maintained: these values were the coordinates in the sequential design for the analysis. At each analysis, one point was drawn on the triangle shown in figure 1 and the global results for efficacy and safety were presented to the Data and Safety Monitoring Review Board. The pattern of all the points created was termed the sample path. When this path remained inside the triangle, the study had to be continued but if the sample path increased or decreased, the study had to be stopped. The sequential analyses were computed by PEST version 2.2. Other qualitative data were analyzed by the chi-square test or Fisher’s exact test, and the Student’s t test was used for quantitative data. All tests were two-tailed with a 5% level of significance. These analyses were performed on the statistical software SAS version 6.08.

Results
From March 1993 to July 1994, 170 patients, 85 in each treatment group, having undergone THR under spinal anaesthesia, were included in the study and received at least one dose of the study medication. These patients were all considered in the safety analysis. Seven of the 170 patients were ongoing at the time of the decision to stop the inclusion recommended by the Data and Safety Monitoring Board. They were considered as overrunning patients and did not appear in the third sequential analysis (n = 163). Among the 170 included patients, 17 patients (seven in the LMWH group and 10 in the control group) were not considered in the intent-to-treat analysis of efficacy, because venography could not be performed (12 patients: four in the LMWH group and eight in the control group) or because venography was found to be inadequate by the review committee (five patients: three in the LMWH group and two in the control group). Finally, a total of 153 patients were analyzed on an intent-to-treat basis (78 in the LMWH group and 75 in the control group). The two treatment groups did not differ in baseline characteristics, excepted for gender (table 1). This factor, which was taken into account in the primary analysis of efficacy, was not found to affect the results of this analysis. The main characteristics of the surgical and anaesthetic procedure are presented in table 2.

THROMBOEMBOLIC COMPLICATIONS
There were no deaths or clinical pulmonary emboli during the study. A total of 39 patients of the 153 evaluable patients (25.5%) presented with venogram-proved DVT of the lower extremities (table 3). Most were asymptomatic and only two
patients (one patient in each group) presented clinical signs of DVT which were confirmed by venography. Overall, the incidence of venous thrombosis on day 10±2 was 14.1% in the LMWH group (95% confidence interval 6–22%), compared with 37.3% (25–47%) in the control group. This difference was statistically significant (P=0.0016) for the triangular test corrected according to the 5% significance level adopted (table 3). None of the 17 excluded patients who did not undergo adequate venography were found to present with clinical signs suggesting DVT. No patient variable was found to affect overall comparison of efficacy outcome of the evaluable patients between the two treatment groups. Of the 39 DVT, eight were bilateral, 20 were in the operated legs and 11 were on the opposite side. Most were detected on systematic examination in the operated legs and 11 were on the opposite leg. Most were detected on systematic examination in the operated legs and 11 were on the opposite leg.

**BLEEDING COMPLICATIONS**

No gross neurological sequelae were observed. Overall, major haemorrhage occurred in 1.2% and minor haemorrhages, including wound haematomas smaller than 1 cm, in 31.2% of patients (table 4). Two patients were considered to present with major haemorrhage: one patient in the LMWH group presented with postoperative haemorrhage at the surgical site on day 6, with a decrease in haemoglobin concentration of more than 4 g dl⁻¹, and requiring transfusion of 2 u. of packed red blood cells; and one patient in the control group presented with postoperative haemorrhage on day 3 through wound drainage with a decrease in haemoglobin concentration of more than 4 g dl⁻¹ and requiring transfusion of 2 u. of packed red blood cells, but no reintervention. Thirty-two patients in the LMWH group (37.6%) and 21 patients in the control group (24.7%) experienced minor haemorrhage (P=0.04). Haemorrhage did not lead to surgical reoperation or premature discontinuation of the study in any patient. There were no differences between the two groups in perioperative blood loss (table 4). Of the 170 patients, 23 received homologous transfusions (13.5%): 16 in the LMWH group and seven in the control group (P=0.044).

**OTHER ADVERSE EVENTS (FROM DAY 1 TO DAY 10±2)**

There were no study withdrawals as a result of adverse events other than DVT or haemorrhages. A total of 45 patients with an unexpected adverse event were observed during the study: 24 patients in the LMWH group and 21 patients in the control group. The principal causes were subluxation of prosthesis in three patients requiring reintervention under general anaesthesia, symptomatic anaemia requiring transfusions in 11 cases, infection (wound infection or general infection) in 12 patients and other symptoms in 19 patients. Among the total number of unexpected adverse event, only five cases (three in the LMWH group and two in the control group) were considered as “possibly” or “probably” related to the study treatment. The remaining cases were considered as mild to moderate in intensity, and resolved within a few days even though the study treatment was maintained.

**3-MONTH FOLLOW-UP PERIOD (FROM DAY 12 TO DAY 90)**

A total of 169 patients (85 in the LMWH group and 84 in the control group) underwent post-surgical follow-up at 3 months (one patient was lost to follow-up). No deaths or thromboembolic events were observed during this period. Fourteen patients presented with further adverse events: six in the LMWH group and eight in the control group. The principal causes were subluxation of prosthesis after day 10 in four patients requiring reintervention under general anaesthesia, infection in two patients and other symptoms in eight patients.

**LABORATORY TESTS**

There were no significant differences between the two groups in absolute and relative changes in red cells and haemoglobin concentration from day 0 to day 10 in four patients requiring reintervention under general anaesthesia, infection in two patients and other symptoms in eight patients.

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**Table 3** Incidence of venogram-proved DVT on day 10±2.

<table>
<thead>
<tr>
<th>Thrombus site</th>
<th>LMWH (n=78)</th>
<th>Placebo (n=75)</th>
<th>Overall (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT</td>
<td>2</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>8</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Muscular VT</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total DVT**</td>
<td>11 (14.1%)</td>
<td>28 (37.3%)</td>
<td>39 (25.5%)</td>
</tr>
</tbody>
</table>

**Table 4** Bleeding complications (mean (SD) or number)

<table>
<thead>
<tr>
<th></th>
<th>LMWH</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal haematoma (n)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major haemorrhages (n)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Wound haematomas (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1–5 cm</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>17</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>20</td>
<td>0.04</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>395 (133.1)</td>
<td>422 (122.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Postoperative blood loss (ml)</td>
<td>783.4 (409.4)</td>
<td>790.4 (381.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>Global calculated blood loss (ml)</td>
<td>1538 (928.9)</td>
<td>1399.7 (928.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Transfusion rate (day 1 to day 12)</td>
<td>18.8%</td>
<td>8.2%</td>
<td>0.044</td>
</tr>
</tbody>
</table>
day 10±2. No thrombocytopoenia occurred in the postoperative period.

Discussion

We have demonstrated that in patients undergoing THR under spinal anaesthesia, the use of LMWH prophylaxis associated with gradual compression stockings significantly decreased the incidence of DVT. The combination of spinal anaesthesia and gradual compression stockings alone, without LMWH, did not provide sufficient antithrombotic prophylaxis. No symptomatic pulmonary emboli were observed in either group.

Many clinical studies and meta-analyses have established that the use of LMWH is associated with an improved benefit/risk ratio compared with unfractionated heparin or oral anticoagulants in orthopaedic surgery. Spinal or extradural anaesthesia has also been shown to decrease the incidence of postoperative DVT.

This effect can be explained by the vasodilatation induced by the pharmacological blocking of the sympathetic system resulting in increased venous blood flow in the lower extremities, the effect of local anaesthetics and subsequent haemodilution. This has been confirmed recently in a review by Prins and Hirsh in fracture and elective hip surgery.

Despite a reduction in the incidence of postoperative DVT (without prophylaxis) of 46–55%, this effect remains controversial.

Another study in THR patients showed a much lower incidence of venogram-proved DVT (12%) after operation under extradural anaesthesia. In patients with a fractured hip, a meta-analysis recently reported a risk reduction (odds ratio) for DVT four times lower with spinal anaesthesia in comparison with general anaesthesia, and a prospective study in patients treated before and after operation with LMWH was unable to find any difference in the rate of DVT between patients operated on under general anaesthesia and those who underwent central neural block. The antithrombotic effect is probably less than that reported initially by Modig and colleagues. Our study represents one of the largest DVT prophylaxis studies in patients operated on under central neural block. Despite the use of central neural block, associated with gradual compression stockings, the incidence of DVT was 37.3% in the control group on day 10±2 after operation. A placebo group was considered to be justified because of the following reasons: all patients wore gradual compression stockings which, although insufficient in high-risk patients, have a proven antithrombotic effect; patients were monitored closely by daily clinical examination, by Duplex scanning performed on day 3 and day 6, and by bilateral ascending venography performed on day 10±2; sequential analysis was performed after every 50 patients in order to assess blindly the DVT rate in both groups, so that the study could be interrupted as soon as a significant difference was noted between the two groups.

In our study, LMWH prophylaxis significantly reduced the rate of DVT to 14.1%, which is close to the generally reported incidence in such patients. Although in Europe the dosage regimen of enoxaparin 40 mg s.c once daily, beginning before operation, is commonly approved for the prevention of postoperative DVT in THR patients, a regimen beginning after operation was chosen in accordance with the recommendations issued by the consensus conference for thromboembolic diseases held in 1991. The risk of extradural or subarachnoid haematoma induced by preoperative LMWH and central neural block is probably very low. Tryba estimated the risk for a spinal haematoma after central neural block to be 1:150 000 after extradural anaesthesia and 1:220 000 after spinal anaesthesia. However, the severity of neurological consequences has to be considered carefully and case reports are still published. A recent literature search reported 61 cases of extradural or spinal haematoma involving central neural block. Forty-two patients had a clotting disorder or were treated with anticoagulants without specification of dose. This incidence is probably underestimated because many of these cases are not reported. This study was not designed specifically to assess the risk of spinal haemorrhage with the combination of LMWH and central neural block, as specific neurological assessments were not performed and the study population was too small to demonstrate a valid difference in the incidence of spinal haematoma. Although no clinical symptoms suggesting a spinal haematoma were observed in our study, the use of extradural or spinal anaesthesia in patients receiving a preoperative dose of LMWH remains a concern.

The frequency of postoperative bleeding complications, including wound haematoma, is believed to increase in heparin-treated patients. This is the main reason for the reluctance of many surgical teams to use heparin prophylaxis. The results of this study confirmed this observation, although there was no difference between the two groups in the incidence of major haemorrhage. Patients in the LMWH group experienced significantly more wound haematomas than in the control group. However, there were no discontinuations of study treatment or surgical reinterventions related to haematoma in either group. The standard postoperative blood loss calculation taking into consideration the perioperative period until day 3, showed no difference between the two groups. However, the global transfusion rate observed in this study appeared lower than that reported for THR surgery. This could be explained by the type of anaesthesia as noted in a recent meta-analysis. When comparing the transfusion rate between the two groups, the observed difference was in favour of the control group, as expected.

In conclusion, spinal anaesthesia during THR surgery in association with gradual compression stockings alone was not sufficient to protect against the risk of postoperative DVT. The addition of LMWH beginning after operation reduced the risk of venogram-proved DVT and demonstrated an acceptable benefit/risk ratio compared with placebo.
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References