Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin

A total of 1290 patients were enrolled in a randomized multicentre double blind study in order to investigate the use of two doses of a new low molecular weight heparin, Logiparin, in the prevention of deep vein thrombosis (DVT) in general surgery. Patients who were included had no contraindication to heparin therapy and had at least one of the recognized risk factors for DVT. Patients were randomized to receive unfractionated heparin (UH) 5000 units b.d., Logiparin 2500 units daily or Logiparin 3500 units daily. Each treatment was given subcutaneously 2h before surgery and continued for 7-10 days. Daily 125I-labelled fibrinogen uptake test (FUTs) were performed from day 2 to day 7 to detect DVT, and phlebography was used to confirm the diagnosis. The wound was examined on a daily basis to check for haematoma formation, and all patients were followed up for 1 month after operation. All three treatment arms were well matched for age, sex, weight, diagnosis and type of operation performed. The three major inclusion criteria in the trial were malignancy, age over 60 years and a history of varicose veins. Positive FUTs (UH = 4.2 per cent, Logiparin 2500 units daily = 7.9 per cent, Logiparin 3500 units daily = 3.7 per cent) and positive angiograms (UH = 3.0 per cent, Logiparin 2500 units daily = 5.6 per cent, Logiparin 3500 units daily = 2.3 per cent) were significantly more common in the Logiparin 2500 units daily group than in the UH and Logiparin 3500 units daily groups. The rates of major complications (severe haemorrhage, death, pulmonary embolism, reintervention) were similar in the three groups.

The value of low-dose heparin (5000 units b.i.d. or t.i.d.) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism in general surgical patients has been extensively evaluated. A recent overview has confirmed the efficacy of such a treatment which typically reduced the risk of DVT from 22.4 per cent to 9 per cent and of pulmonary embolism from 3 per cent to 1.7 per cent. In the past few years new molecules of heparin with low molecular weight have been introduced. These have interesting new biological properties and they have been alleged in practice to be superior to standard heparin (UH). Several compounds have been developed and have been or are currently being evaluated in patients1-8. An investigation was undertaken to assess the prophylactic value on DVT of a new low-dose low molecular weight heparin, Logiparin®, Novo Nordisk, Copenhagen, Denmark as compared with a standard heparin regimen in middle/high risk patients undergoing major general surgery. In addition, since a major problem in clinical trials with low molecular weight heparin is the choice of dose because no biological test allows a truly reliable indicator of its antithrombotic action, two doses of Logiparin were compared concomitantly with UH. The protocol was accepted by the Université Claude Bernard Ethical Committee.

Patients and methods

Patient selection
Between June 1987 and November 1988, patients were recruited from 23 centres located both in France and in the UK. Patients undergoing general surgery (abdominal, gynaecological, urological or thoracic but not cardiac surgery) who were 40 years or older and in whom general anaesthesia longer than 30 min was anticipated were selected. Informed consent was obtained in all cases. Only patients with at least one of the following risk factors for thromboembolic disease were included in the trial: previous history of venous thromboembolism, varicose veins, obesity (overweight >20 per cent), contraceptive pill or hormonal replacement therapy, chronic respiratory insufficiency, heart failure, previous long bone fracture of lower limb, bed rest >5 days before surgery, predicted duration of surgery >4 h, age >60 years.

Study treatments
There were three treatment regimens in the trial: Logiparin 2500 units once a day (the preparations contained 8333 anti Xa units/ml), Logiparin 3500 units once a day (the preparations contained 11 667 anti Xa units/ml), and Heparin Novo 5000 units b.d. (sodium heparin prepared from hog intestinal mucosa). As Logiparin was given only once daily a second injection was given daily (0.9 per cent NaCl) to ensure that all three regimes were 'blind'. Two hours before surgical intervention patients received a morning injection of the allocated treatment. The second injection was given 12 h later as an evening injection, and injections then followed every 12 h. All treatments were administered by subcutaneous injection. Treatment was continued for at least 7 days and for a maximum of 10 days. If thromboembolic prophylaxis was required for more than 10 days, UH was used according to usual clinical practice. Premature discontinuation of the study treatment was considered as a critical event and documented accordingly. Stockings or other forms of DVT prophylaxis were not allowed during the study period.
Study design
A randomized double blind trial was organized by a Coordinating Centre, a Steering Committee, a Critical Event Committee (which assessed major events) and an Executive Committee (operational arm of the Steering Committee).

After baseline examination and assessment of eligibility, the investigator transmitted a request for allocation by computer network to the Coordinating Centre. After checking eligibility the computer investigator transmitted a request for allocation by computer network. The advantages of such a process, and on-line editing and correction.

Evaluation of end-points and clinical follow-up
A fibrinogen uptake test (FUT) was performed daily from day 2 to day 7 or 8. On Sundays and holidays the scan was performed only if a positive test was observed on the previous day, there should not have been more than one day missing in a series of scans for a given patient and the series should have contained at least six tests if none was positive.

Two criteria were necessary for a positive scan: 20 per cent relative increase between one point and the highest adjacent point or the contralateral point, and persistence of increase on the next day. Assessment of FUT was first done locally after which data from all points were circulated through a computer network. The advantages of such a process, and on-line editing and correction.

Results
Patients
Study population. A total of 1290 patients were randomly allocated to receive either SH (429 patients), Logiparin 2500 units daily (431 patients) or Logiparin 3500 units daily (430 patients). Clinical and biological baseline characteristics were fairly well balanced between the three groups; 45 baseline characteristics were compared and no biological or clinical comparison reached P = 0.05 level. There were 513 men and 777 women and the mean age was 61 years (Table 1). The mean number of risk factors for each patient at entry to the study was 2.3.

Protocol deviations. Twenty-seven patients did not have any FUT. Surgery was cancelled in seven and FUTs were not performed in a further 20 (SH, n = 8; Logiparin 2500 units daily, n = 8; Logiparin 3500 units daily, n = 11). All 27 patients are nevertheless accounted for in the main analysis on an intention to treat basis.

Discontinuation of study treatment before day 8. In addition to the patients who did not receive any injection of study treatment, 68 others prematurely stopped this treatment (one of these patients was not operated on but received the first presurgical injection). The causes for discontinuation are shown in Table 2.

Primary efficacy analysis
Incidence of venous thrombosis confirmed by phlebography. Positive FUT scans reported locally led to phlebography in 94 patients (four had two angiograms performed). Out of 64 patients with a central positive FUT reading, three did not have phlebography performed (because the patient or the surgeon refused) and for six patients the films were lost by the local hospital and could not, therefore, be centrally analysed.

The results of FUT scans and angiography as assessed by the Central Angiography Reading Committee are shown in Tables 3 and 4; no statistically significant difference between the three groups was observed with respect to the incidence of DVT at day 8. However, if all types of venous thrombosis are accounted for (superficial and/or deep), there was a significantly higher incidence of vein thrombosis in the
Biology

Anti-Xa analysis. All the measurements were performed blindly in a central laboratory using an amidolytic technique with both SH and low molecular weight heparin standards. At baseline, factor Xa activity was similar in the three groups. On day 3, 3 h and 10 h after injection, on day 5 and on discharge, factor Xa activity was significantly higher in the low molecular weight heparin groups than in the UH group, and higher in the Logiparin 3500 units daily group than in the Logiparin 2500 units daily group (Figure 1).

Discussion

The present study was designed to evaluate the potential benefit of Logiparin in preventing DVT in patients after surgery compared with low-dose standard heparin, to provide information about the best prophylactic dosage of Logiparin and to evaluate the safety of this medication. The results indicate that there was no difference in the efficacy of Logiparin 3500 units daily and SH 5000 b.d. in preventing postoperative DVT while Logiparin 2500 units daily was significantly less effective than SH and Logiparin 3500 units daily. The efficacies of Logiparin 3500 units and UH were very similar and led to a low incidence of venous thrombosis. The results are consistent whether one looks at FUT positive tests, any venous thrombosis on phleboangiography or DVT on phleboangiography. The three regimens were well tolerated and there was no difference between the groups in the incidence of major as well as minor undesirable effects. The efficacy and tolerance of Logiparin 3500 units daily compared with UH are consistent with the result observed in previous trials with other low molecular weight heparins.

List of participants

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Logiparin versus standard heparin in general surgery: H.B.P.M. Research Group

More than 10 years ago and the present management of surgical patients, surgical techniques, early mobilization and physiotherapy may contribute to the lower incidence of venous thrombosis seen in the present study. In more recent randomized trials, comparing UH and low molecular weight heparins in general surgery, the incidence of positive FUT in the SH groups ranged from 11.9 per cent to 0 per cent.

Evaluation of the safety of the treatment was one of the secondary aims of the trial. Since haemorrhage is a major concern during anticoagulant therapy, one of the hoped for benefits of low molecular weight heparin was a reduction in bleeding complications. Some studies have reported an increase in bleeding complications with low molecular weight heparins. The doses might have been too high in these studies. The choice of the appropriate dose should be made cautiously in view of both the results on DVT and possible side effects. Whether standardization of the units of low molecular weight heparin will help in clarifying the choice of the prophylactic dose is still uncertain since no clear relationship between anti-Xa activity and efficacy as well as side effects has truly been demonstrated. This trial is the first to address the question of the appropriate dose based on clinical end-points. However, practical limitations due to sample size did not allow a study of a wider range of Logiparin doses.

In conclusion, the results of this study demonstrate a significant difference in the efficacy of two doses of Logiparin compared with UH in the prevention of venous thrombosis in surgical patients. Logiparin 2500 units daily was less effective than SH and Logiparin 3500 units daily. The efficacies of Logiparin 3500 units and UH were very similar and led to a low incidence of venous thrombosis. The results are consistent whether one looks at FUT positive tests, any venous thrombosis on phleboangiography or DVT on phleboangiography. The three regimens were well tolerated and there was no difference between the groups in the incidence of major as well as minor undesirable effects. The efficacy and tolerance of Logiparin 3500 units daily compared with UH are consistent with the result observed in previous trials with other low molecular weight heparins.
Table 1. Disposition of the study treatment

<table>
<thead>
<tr>
<th></th>
<th>Unfractionated heparin (n = 429)</th>
<th>Logiparin 2500 units daily (n = 431)</th>
<th>Logiparin 3500 units daily (n = 420)</th>
<th>Total (n = 1290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No study treatment</td>
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<tr>
<td>Operation cancelled</td>
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<tr>
<td>Impossibility (no consent, discharge)</td>
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<tr>
<td>Haemorrhage</td>
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<tr>
<td>Other side effect</td>
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<tr>
<td>Deep vein thrombosis suspected</td>
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<td>Indication of high doses of anticoagulant</td>
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<tr>
<td>Contraindication to anticoagulation</td>
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<tr>
<td>Total</td>
<td>25</td>
<td>35</td>
<td>28</td>
<td>88</td>
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</table>

Table 2. Positive fibrinogen uptake test

<table>
<thead>
<tr>
<th></th>
<th>Unfractionated heparin (n = 429)</th>
<th>Logiparin 2500 units daily (n = 431)</th>
<th>Logiparin 3500 units daily (n = 420)</th>
<th>Total (n = 1290)</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>16 (37)</td>
<td>33 (77)</td>
<td>15 (35)</td>
<td>64 (50)</td>
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<tr>
<td>Positive or doubtful</td>
<td>18 (42)</td>
<td>34 (79)</td>
<td>16 (37)</td>
<td>68 (53)</td>
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</table>

Global comparison using χ² test. Values in parentheses are percentages.

Table 3. Central evaluation of angiography

<table>
<thead>
<tr>
<th></th>
<th>Standard heparin (n = 429)</th>
<th>Logiparin 2500 units daily (n = 431)</th>
<th>Logiparin 3500 units daily (n = 420)</th>
<th>Total (n = 1290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial or DVT before day 8</td>
<td>13 (30)</td>
<td>24 (56)</td>
<td>10 (23)</td>
<td>47</td>
</tr>
<tr>
<td>DVT before day 8</td>
<td>7 (16)</td>
<td>16 (37)</td>
<td>7 (16)</td>
<td>30</td>
</tr>
<tr>
<td>Superficial or DVT during the 1-month follow-up</td>
<td>15 (35)</td>
<td>26 (60)</td>
<td>11 (26)</td>
<td>52</td>
</tr>
</tbody>
</table>

Global comparison using χ² test. Values in parentheses are percentages; DVT, deep vein thrombosis.

Logiparin 2500 units daily group. Five additional patients had phlebography performed after discharge for a clinically suspected phlebitis, but the results of these angiograms did not affect the overall results (Table 4).

The effect of treatment on venous thrombosis was also evaluated in a multivariate analysis with the main risk factors as covariates (varicose veins, obesity, malignancy, age >60 years). A significant negative effect was still present for Logiparin 2500 units daily (P = 0.01). No significant difference was observed between UH and Logiparin 3500 units daily (P = 0.52).

Secondary efficacy analysis

Positive FUT. Sixty-four FUT tests were confirmed as positive by the Central Reading panel. Global comparison using the χ² test between the three groups for positive FUT shows a statistically significant difference (P = 0.007). However, the results of the SH group and the Logiparin 3500 units group are similar (3.7 per cent and 3.5 per cent) (Table 3).
Luparin versus standard heparin in general surgery: H.B.P.M. Research Group

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References