Background: Pulmonary embolism (PE) occurs in 50% or more of patients with proximal deep-vein thrombosis. Low-molecular-weight heparin treatment is effective and safe in patients with deep vein thrombosis and may also be so in patients with PE. Recent rigorous clinical trials have established objective criteria for determining a high probability of PE by perfusion lung scanning.

Objective: To compare low-molecular-weight heparin with intravenous heparin for the treatment of patients with objectively documented PE and underlying proximal deep vein thrombosis.

Methods: In a multicenter, double-blind, randomized trial, we compared fixed-dose subcutaneous low-molecular-weight heparin (tinzaparin sodium) given once daily with dose-adjusted intravenous heparin given by continuous infusion using objective documentation of clinical outcomes. Pulmonary embolism at study entry was documented by the presence of high-probability lung scan findings.

Results: Of 200 patients with high-probability lung scan findings at study entry, none of the 97 who received low-molecular-weight heparin had new episodes of venous thromboembolism compared with 7 (6.8%) of 103 patients who received intravenous heparin (95% confidence interval for the difference, 1.9%-11.7%; P = .01). Major bleeding associated with initial therapy occurred in 1 patient (1.0%) who was given low-molecular-weight heparin and in 2 patients (1.9%) given intravenous heparin (95% confidence interval for the difference, −2.4% to 4.3%).

Conclusions: Low-molecular-weight heparin administered once daily subcutaneously was no less effective and probably more effective than use of dose-adjusted intravenous unfractionated heparin for preventing recurrent venous thromboembolism in patients with PE and associated proximal deep vein thrombosis. Our findings extend the use of low-molecular-weight heparin without anticoagulant monitoring to patients with submassive PE.

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PATIENTS AND METHODS

STUDY DESIGN

The American-Canadian Thrombosis Study\(^4\) was a multicenter, randomized, double-blind clinical trial comparing unfractionated continuous intravenous heparin therapy with once-daily subcutaneous low-molecular-weight heparin therapy in patients with acute proximal DVT. The protocol mandated objective testing for PE in all patients at study entry. Fifteen centers in the United States and Canada participated in the trial. The protocol was approved by the institutional review board at each center.

PATIENTS

Consecutive eligible patients aged 18 years and older with proximal DVT (thrombosis of the popliteal or more proximal veins of the legs) documented by venography were enrolled in the study. Patients were eligible if they had none of the following: active bleeding or disorders contraindicating anticoagulant drug therapy; allergy to heparin, bisulfites, or fish; pregnancy; 2 or more previously documented episodes of DVT or PE; history of protein C deficiency; history of heparin-associated thrombocytopenia; severe malignant hypertension (diastolic blood pressure ≥130 mm Hg); severe hepatic failure (hepatic encephalopathy); severe renal failure necessitating dialysis; or geographic inaccessibility preventing follow-up visit attendance. Eligible patients were excluded if they received treatment with warfarin sodium, low-molecular-weight heparin, or heparinoids within 7 days before study entry; if they received treatment with therapeutic subcutaneous heparin within the preceding 12 hours; were receiving intravenous heparin; or if they declined to give written informed consent.

Before randomization, patients were stratified into groups according to the study center where they were treated, presence or absence of previous VTE, and presence or absence of 1 or more risk factors for bleeding (sur- gery within the previous 14 days, history of peptic ulcer disease, thrombotic stroke within the previous 14 days, and a platelet count of <150 × 10^9/L). A randomized, computer-derived treatment schedule was used to assign patients to receive intravenous heparin or subcutaneous low-molecular-weight heparin. Within each stratum, the randomization schedule was balanced in blocks of 4.

Approximately 50% to 60% of patients with acute proximal DVT had asymptomatic PE at presentation.\(^3,4\) Perfusion lung scanning was performed on study entry to document the presence of PE and to compare against lung scan abnormalities found at any subsequent presentation with symptoms or signs of PE.

In each patient, anticoagulant drug therapy was started as soon as possible after proximal DVT had been documented objectively, by ascending contrast venography\(^8,11\) or by impedance plethysmography\(^6,11\) or B-mode imaging using venous compression.\(^18,27,28\) In patients studied by these noninvasive methods, the diagnosis was also confirmed as soon as possible by venography.

REGIMENS

Patients in the intravenous heparin group received an initial bolus dose of 5000 US Pharmacopeia units of heparin followed by continuous intravenous infusion of heparin. The initial dose was 40 320 U every 24 hours for patients without the designated risk factors for bleeding and 29 760 U every 24 hours for those with 1 or more designated risk factors. The doses were chosen to minimize the risk of insufficient heparin treatment during the first 24 hours of therapy\(^22,28,32\) and to avoid high initial doses of heparin in patients with designated risk factors for bleeding.\(^30\)

The dose of intravenous heparin was adjusted according to the results of laboratory monitoring using the activated partial thromboplastin time (APTT). This was obtained 4 hours after starting heparin administration and was repeated every 4 to 6 hours until the result was within the prescribed therapeutic range (≈1.5 to 2.5 times the mean control value of 30 seconds obtained with a thromboplastin reagent [Actin FS; Dade Behring, Deerfield, Ill]). Thereafter, the APTT was measured once daily; if the result was subtherapeutic, the test was repeated every 4 hours until the therapeutic range was regained.

Patients receiving low-molecular-weight heparin were given a fixed dose of 175 International Factor 3a Inhibitory Units per kilogram of body weight subcutaneously once every 24 hours. This regimen was chosen because results of pharmacokinetic studies in normal subjects demonstrated unnecessary because of a predictable anticoagulant response when administered subcutaneously in weight-based doses.\(^34,36,44\) Low-molecular-weight heparin treatment has been shown\(^45-52\) to be effective and safe in patients with DVT and may also be so in patients with PE.

We conducted a double-blind, randomized trial comparing low-molecular-weight heparin (tinzaparin sodium) with intravenous heparin treatment in patients with objectively documented proximal DVT.\(^49\) A priori, all patients underwent baseline lung scanning, and those with subsequent episodes of suspected recurrent VTE underwent repeated objective testing. Recent rigorous clinical trials\(^18,33-35\) have established objective criteria for determining a high probability of PE by perfusion lung scanning. Almost half (47.7%) of the study population (200 of 419 patients) had high-probability lung scan findings at randomization. This finding and the randomized trial design allowed us to compare low-molecular-weight heparin vs unfractionated heparin treatment in patients with objectively documented PE and proximal DVT. Our objective was to determine whether low-molecular-weight heparin administered subcutaneously once daily without anticoagulant monitoring is effective and safe in such patients.

RESULTS

PATIENTS

Of 432 consecutive patients with proximal DVT enrolled in the study, 419 (97.0%) underwent lung scans. Of these 419 patients, 200 (47.7%) had high-probability
that it produced a sustained anticoagulant response (anti-factor Xa activity) throughout the 24-hour dosing period and did not produce a substantial accumulation of the anticoagulant effect when given for 5 to 6 days.

All patients received long-term therapy with warfarin sodium for at least 3 months. The initial dose was 10 mg given on the second day of initial therapy, which was then adjusted to maintain the international normalized ratio between 2.0 and 3.0. After the first 6 days, the dose was adjusted weekly by the patient’s primary care physician. Treatment with intravenous heparin or subcutaneous low-molecular-weight heparin was discontinued on the sixth day provided that the international normalized ratio was 2.0 or more.

The study used a double-blind design. Patients who were randomly assigned to receive intravenous heparin also received a subcutaneous placebo injection once every 24 hours. Patients assigned to receive subcutaneous low-molecular-weight heparin also received an intravenous placebo bolus and a continuous intravenous infusion of placebo throughout initial therapy. To maintain double-blinding, APTTs were reported only to a member of the health care team not involved in assessing the patient’s outcome. The APTT was not recorded on the patient’s medical chart during the study or reported to any other member of the health care team. Adjustments in the rate of intravenous infusion of heparin or placebo were made by an unblinded physician according to dosing schedules established before the trial began.

Use of drugs containing aspirin was prohibited during the study. Use of sulfinpyrazone, dipyridamole, and indomethacin was strongly discouraged.

**SURVEILLANCE AND FOLLOW-UP**

All patients were examined daily during initial therapy; symptoms or signs of recurrent DVT, PE, or bleeding were sought. Perfusion lung scanning was performed in all patients within 48 hours of study entry. The diagnosis of PE on study entry was established according to published criteria for perfusion lung scanning. When a subsequent episode of PE was suspected based on clinical signs or symptoms, the diagnosis was confirmed by lung scanning (indicating a new perfusion defect with a high probability of PE) or by pulmonary angiography (revealing a constant intraluminal filling defect on multiple films) performed when lung scanning did not indicate a high probability of PE. All patients were followed up for 3 months to assess whether inadequate initial therapy could lead to recurrent thromboembolism during long-term therapy with warfarin. Patients were asked to go to the hospital immediately if symptoms or signs of recurrent DVT or PE developed. Patients with suspected recurrent PE underwent objective testing as described immediately above. Those with suspected recurrent venous thrombosis underwent impedance plethysmography and venography; the diagnostic criteria are described elsewhere.

Bleeding was classified as major or minor according to criteria described elsewhere. Data on the outcome measures of effectiveness (recurrent VTE), safety (bleeding complications), and patient deaths were interpreted by a central adjudicating committee. Adjudication was made by 2 committee members not involved in the patient’s care; disputes were resolved independently by a third. Objective test results were interpreted independently and without the interpreter’s knowledge of the patient’s other results, clinical findings, or treatment group.

**STATISTICAL ANALYSIS**

We estimated that a sample of 200 patients per group would be large enough that a 93% confidence interval for the difference in frequencies of recurrent VTE would exclude a true difference of 3% or more, assuming observed frequencies of 3% in both treatment groups. Uncorrected chi-square and Fisher exact tests were used to compare the frequencies of death, recurrent VTE, and bleeding in both treatment groups. Ninety-five percent confidence limits for the true incidences of recurrent VTE and bleeding complications were calculated from the binomial distribution. Confidence intervals for the difference between the 2 treatment groups in the incidence of recurrent VTE and bleeding complications were calculated using the normal approximation to the binomial distribution. The log-rank test was used to assess differences in the cumulative incidence of death and recurrent VTE.

Values for the APTT and anti-factor Xa levels obtained in a given test are displayed as box plots.

**RECURRENT VTE**

Frequencies of recurrent VTE are shown in Table 2. All patients presented with overt signs and symptoms of VTE. Analysis using the log-rank test, which takes into account the length of time to an event, indicated a statistically significant difference (P = .009) between groups in the frequency of recurrent thromboembolic events (Table 2 and Figure 1).

Of 7 patients in the intravenous heparin group with new episodes of VTE, 4 had new episodes of PE (all identified by new high-probability lung scan findings). Recurrent venous thrombosis was documented by venography in 1 patient and by impedance plethysmography in the remaining 2. The APTT during initial heparin treatment was in the therapeutic range in 6 of 7 patients. Dur-
ing long-term follow-up, subtherapeutic prothrombin times were noted before or at the time of the recurrent thromboembolic event in only 2 of 7 patients who were receiving intravenous heparin. There were no episodes of recurrent VTE during initial treatment or long-term follow-up of patients receiving low-molecular-weight heparin.

BLEEDING COMPLICATIONS

The frequency of bleeding complications during or immediately after initial treatment is shown in Table 2. Type of bleeding and predisposing disorders are shown in Table 3.

Major bleeding occurred in 1 patient (1.0%) receiving low-molecular-weight heparin and in 2 (1.9%) receiving intravenous heparin (neither patient had an APTT in the supratherapeutic range) (Table 2).

Minor bleeding occurred in 1 patient (1.0%) receiving low-molecular-weight heparin and in 3 (2.9%) receiving intravenous heparin (the APTT was in the supratherapeutic range in 2 of the 3 patients) (Table 2).

Type of bleeding and predisposing disorders for bleeding complications that occurred during long-term warfarin therapy and remote from initial therapy are shown in Table 4. Major bleeding remote from the time of initial therapy occurred during long-term warfarin therapy in 3 patients (3.1%) receiving low-molecular-weight heparin and in none receiving intravenous heparin. The bleeding was a muscle hematoma on day 56 and hematemesis on days 24 and 51. The international normalized ratio was more than 3.0 at or before bleeding in 2 of the 3 patients.

Minor bleeding remote from the time of initial therapy occurred during long-term warfarin therapy in 3 patients (3.1%) receiving low-molecular-weight heparin (hemoptysis, vaginal bleeding, and hematuria on days 23, 38, and 44, respectively) and in 3 (2.9%) receiving intravenous heparin (hematochezia, epistaxis, and hematochezia on days 41, 49, and 67, respectively). The international normalized ratio was more than 3.0 at or before bleeding in 1 of 3 patients receiving low-molecular-weight heparin and in 1 of 3 receiving intravenous heparin.

DEATH

The proportions of patients who died are shown in Table 2. The causes and timing of death are shown in Table 5.

THROMBOCYTOPENIA

Three patients (3.1%) taking low-molecular-weight heparin and 1 (1.0%) taking intravenous heparin had thrombocytopenia.
ANALYSIS OF APTTs AND Xa LEVELS

The APTTs are shown in Figure 2, and the chromogenic Xa assay results are shown in Figure 3 for all patients during initial therapy.

COMMENT

Our findings demonstrate that low-molecular-weight heparin administered once daily subcutaneously was no less effective and probably more effective than dose-adjusted intravenous unfractionated heparin treatment for preventing recurrent VTE in patients with PE and associated proximal DVT. Low-molecular-weight heparin therapy has the advantage of using a fixed dose of weight-based antithrombotic therapy (thus avoiding the potential pitfalls of anticoagulant monitoring and dose adjustment inherent with unfractionated heparin). Hemorrhagic complications were infrequent in both groups.

Our study evaluated patients with PE documented by high-probability lung scan findings. These emboli were not minor, since by definition, they resulted in perfusion deficits of 75% or more of a lung segment. There was an important risk (6.8%) of recurrent VTE among patients receiving standard treatment with intravenous heparin. Thus, although most patients had symptoms of venous thrombosis rather than PE at study entry, the outcomes on follow-up indicate that our study population was composed of patients with clinically important venous thromboembolic disease consisting of PE and underlying proximal DVT.

Diagnosis of PE at study entry was based on a high-probability interpretation of a perfusion lung scan and a regionally normal finding on a chest radiograph. The report by the American College of Chest Physicians Consensus Committee on Pulmonary Embolism identifies that if the perfusion scan is interpreted as high probability for PE and the chest radiograph findings are regionally normal, a ventilation scan is unnecessary. In the Prospective Investigation of Pulmonary Embolism Diagnosis, using pulmonary angiography as the reference standard, a high-probability perfusion lung scan pattern—combined with a chest radiograph—had a high positive predictive value for acute PE that was no less predictive than a high-probability, combined ventilation-perfusion lung scan finding. As such, we used valid criteria for establishing the presence of PE at study entry.

Table 3. Bleeding Complications During or Immediately After Initial Treatment in the 2 Groups

<table>
<thead>
<tr>
<th>Site of Bleeding</th>
<th>Predisposing Disorder</th>
<th>Patients, No. (n = 7)</th>
<th>Days After Start of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>Infracranial</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Epistaxis</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6, 3, 4</td>
</tr>
</tbody>
</table>

Table 4. Long-term Bleeding Complications After Initial Treatment in the 2 Groups

<table>
<thead>
<tr>
<th>Site of Bleeding</th>
<th>Predisposing Disorder</th>
<th>Patients, No.</th>
<th>Days After Start of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>Infracranial</td>
<td>Gastric ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Hematuria</td>
<td>Colon cancer with secondary metastasis</td>
<td>1, 41</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Hamstring hematoma</td>
<td>Duodenal ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Epistaxis</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Gastrointestinal tract</td>
<td>Quadruplegic</td>
<td>1</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Vaginal</td>
<td>Postexcisional vaginal polyp</td>
<td>1, 38</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Hemothysis</td>
<td>Endobronchial carcinoma</td>
<td>1, 23</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Hematuria</td>
<td>Suprapubic catheter</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5. Causes and Timing of Death in the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Intravenous Heparin Group</th>
<th>Low–Molecular-Weight Heparin Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism (abrupt)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic carcinoma (abrupt)</td>
<td>5, 10, 12, 16, 75, 84</td>
<td>1, 17</td>
</tr>
<tr>
<td>Metastatic carcinoma (insidious)</td>
<td>3, 61, 71, 84</td>
<td>4, 31, 32, 58, 77</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>0</td>
<td>1, 2</td>
</tr>
</tbody>
</table>
The scintigraphic diagnosis of acute PE is compromised in patients with a past history of PE or DVT; the positive predictive value of high-probability lung perfusion scan patterns for PE is considerably less in these patients.53 Most of our patients (82.5%) did not have the confounding history of previous DVT or PE. None of the patients who had recurrent VTE also had a previous history of DVT or PE.

Care was taken throughout the study to ensure that adequate doses of intravenous heparin were administered. The standardized protocol used has been shown to achieve therapeutic levels in 90% or more of patients during the first 24 hours and maintains them thereafter.30 Thus, our results cannot be attributed to inadequate initial therapy with intravenous heparin.

The study was a multicenter, double-blind clinical trial. To avoid a selection bias, care was taken to ensure that participating physicians adhered to the protocol. Before the study, the criteria for eligibility were specified; 51% of eligible patients were randomized. Baseline perfusion lung scanning was mandated a priori and obtained in 97.0% of patients. Well-validated criteria were used to determine the presence of both PE on study entry and of recurrent VTE. The clinical characteristics similar to those in our study—should our findings—were present in a higher proportion of our patients; the event rates in the control group (intravenous unfractionated heparin) for recurrent VTE and death were considerably higher in our study; and our study was double-blind, protecting against diagnostic suspicion bias. Furthermore, the THÉSÉE investigators treated most patients with therapeutic doses of unfractionated heparin before initiating low-molecular-weight heparin treatment; in our study, patients who were randomly assigned to receive low-molecular-weight heparin did not receive unfractionated heparin.

Accordingly, our study had greater power to detect a difference between treatment groups because of the greater burden of illness of the study population, resulting in a higher rate of recurrent thromboembolic events in the unfractionated heparin comparison group. Our findings are strengthened by the findings that patients in either study who received low-molecular-weight heparin (tinzaparin sodium) had a similar low frequency of recurrent VTE.

The therapeutic role of low-molecular-weight heparin in patients with massive PE who are hemodynamically unstable remains to be determined. Most patients in our study presented with symptomatic proximal DVT, and were found on entry by objective testing to have PE; symptoms and signs of PE were identified in only 15% of these patients. For this reason, our findings—although applicable to patients with PE who have clinical characteristics similar to those in our study—should not be generalized to patients with massive embolism who are hemodynamically unstable.
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