Preoperative vs Postoperative Initiation of Low-Molecular-Weight Heparin Prophylaxis Against Venous Thromboembolism in Patients Undergoing Elective Hip Replacement

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Background: Although preoperative and postoperative initiation of prophylaxis for deep vein thrombosis (DVT) with low-molecular-weight heparin (LMWH) are effective, the relative effectiveness and safety of these approaches is unknown. In the absence of a published definitive level 1 trial addressing this question, a meta-analysis is appropriate.

Objective: To report a meta-analysis comparing preoperative with postoperative initiation of prophylaxis of DVT in patients undergoing elective hip replacement.

Methods: Relevant trials were identified, and potential biases in the meta-analysis were minimized by analyzing all rigorously performed randomized trials that met all of the following criteria for conduct of the trial: (1) double-blind design, (2) objective documentation of the frequencies of DVT by ascending contrast venography, (3) venography performed before or at the time of discharge from the hospital, (4) initiation of the same LMWH preoperatively or postoperatively in dosages shown to be effective, (5) compliance with the criteria for a level 1 trial, and (6) objective documentation of major and minor bleeding according to strict criteria.

Results: Treatment with LMWH initiated preoperatively was associated with a DVT frequency of 10.0% compared with a frequency of 15.3% when the LMWH was initiated postoperatively ($P = .02$, Fisher exact test). Major bleeding was less frequent in patients receiving preoperatively initiated LMWH than in patients receiving postoperatively initiated LMWH (0.9%, vs 3.5%; $P = .01$, Fisher exact test).

Conclusions: Our findings support the need for a randomized comparison of preoperative and postoperative initiation of pharmacological prophylaxis of DVT. Such a trial would resolve the divergent practices for DVT prophylaxis between Europe and the North American countries, the United States and Canada, and would affect the treatment for thousands of patients on both continents.

Arch Intern Med. 1999;159:137-141

Epidemiological data have demonstrated that venous thrombosis at the time of surgery or postoperatively is common in high-risk surgical patients. Low-molecular-weight heparin (LMWH) is an effective prophylactic agent for patients undergoing elective hip replacement. Clinical practice has diverged in the North America countries, the United States and Canada, and Europe as to the time for initiation of prophylaxis of deep vein thrombosis (DVT) in high-risk surgical patients. Prophylaxis with LMWH has been evaluated against placebo or active therapy in patients undergoing elective hip replacement in multiple level 1 randomized trials. European trials have evaluated preoperatively initiated prophylaxis with LMWH. The preoperative initiation of prophylaxis of DVT was based on the premise that DVT typically begins at the time of surgery, and that preoperative initiation of prophylaxis is necessary to optimize the antithrombotic effectiveness of the prophylactic agents. In contrast, trials performed in the United States and Canada have evaluated postoperatively initiated prophylaxis with LMWH once surgical bleeding had abated (12-24 hours after surgery). The premise of this approach was to minimize the risk of bleeding. Although preoperative and postoperative initiation of LMWH prophylaxis are effective, the relative effectiveness and safety of these divergent approaches is unknown. To our knowledge, no published trials have directly resolved this key comparison. Indeed, the European consensus group concluded that a key question to be addressed by a level 1 randomized trial is the relative effec-
MATERIALS AND METHODS

LITERATURE SEARCH

Relevant trials were identified by using the following strategy. A MEDLINE computerized database search of the English-language literature was performed for the years 1986 through 1997 by using the following key subject headings: thrombophlebitis, pulmonary embolism, LMWH, enoxaparin, hip prosthesis, prevention, and prophylaxis. Original articles, reviews, and consensus reports were identified. Bibliographies of the published articles and our personal reference files were cross-checked for additional relevant publications.

METHODOLOGICAL CONSIDERATIONS

We minimized potential biases in the meta-analysis by analyzing all rigorously performed randomized trials that met all of the following criteria for the conduct of the trial: (1) double-blind design, (2) objective documentation of the frequencies of DVT by ascending contrast venography in patients undergoing elective hip replacement, (3) venography performed before or at the time of discharge from the hospital, (4) initiation of the same LMWH preoperatively or postoperatively in dosages shown to be effective, (5) compliance with the criteria for a level 1 trial, and (6) objective documentation of major and minor bleeding according to criteria defined a priori and listed in the section “Outcomes.” We defined these criteria for the inclusion of trials before performing the meta-analysis.

The lack of a direct randomized comparison of preoperative vs postoperative initiation of DVT prophylaxis with LMWH necessitated the performance of a meta-analysis. Since it was not feasible to stratify by trial in the analysis, the potential effect of between-trial variation in effectiveness and safety of postoperative vs preoperative initiation of DVT prophylaxis in high-risk surgical patients. The importance of this question is emphasized by the potentially large numbers of patients affected on each continent by the divergent clinical practices. In the absence of a definitive level 1 trial to address this question, a meta-analysis is appropriate. We report a meta-analysis comparing the preoperative with the postoperative initiation of DVT prophylaxis in patients undergoing elective hip replacement.

Meta-analysis has been criticized because of potential weaknesses resulting from the lack of key data in many of the trials included, failure to consider relevant variables, gross heterogeneity in the trials, and bias in the interpretation of data. When applied to the evaluation of LMWH, these include the methodological error of pooling clinical trials of different LMWHs. To avoid this flaw, we confined our analysis to trials evaluating the same LMWH. This was possible because multiple randomized trials evaluating the same LMWH, enoxaparin, in Europe, Canada, and the United States have been published. Other key biases were avoided by addressing only data from level 1 randomized trials that used blind assessment of the outcome and objective documentation of the frequency of DVT and major bleeding. We also required that the trials included in the meta-analysis evaluated dosages of LMWH that had been shown to be effective. Finally, inferences were drawn from the findings that support hypotheses rather than provide directives for clinical practice.

The findings by meta-analysis are surprising. Preoperative initiation of LMWH prophylaxis was not associated with a loss of safety for patients undergoing elective prostatic hip surgery. In addition, it was more effective. These findings have a potential effect for a large number of patients.

RESULTS

The English-language literature included 10 randomized trials evaluating DVT prophylaxis with the LMWH, enoxaparin, in patients undergoing elective hip replacement. These original articles were published in the cited literature from 1986 to 1997.

OUTCOMES

We assessed the outcomes' effectiveness and safety. We assessed effectiveness by using the relative frequencies of venographically documented DVT. Constant intraluminal filling defects in the popliteal, superficial femoral, common femoral, or external iliac veins (with or without constant intraluminal filling defects in the deep veins of the calf) were classified as proximal vein thrombosis. Constant intraluminal filling defects confined to the deep veins of the calf were classified as calf-vein thrombosis. We assessed safety by using the objectively documented episodes of major and minor bleeding. The criteria for major bleeding were as follows: (1) overt bleeding that produced a decrease in the level of hemoglobin of 20 g/L or more, (2) a requirement for transfusion of 2 or more units of blood, (3) retroperitoneal bleeding, (4) bleeding into a major prosthetic joint, or (5) intracranial bleeding. These criteria have been shown to be reproducible, with good interobserver and intraobserver agreement. The criteria for minor bleeding was overt bleeding that did not meet the criteria for major bleeding.

LITERATURE SEARCH AND TRIAL SELECTION

The meta-analysis was based on the simple pooling of results from preoperative and postoperative treatment arms. The Fisher exact test was used to compare the incidence of DVT and the incidence of bleeding of the 2 treatment arms. Confidence intervals for single proportions were based on exact binomial probabilities; for differences in proportions, the normal approximation to the binomial was applied. A level 1 trial was defined as a randomized trial in which the lower limit of the confidence interval for the treatment effect exceeded the minimal clinically important benefit.
Six trials met the methodological criteria for inclusion in the meta-analysis.9,10,15,20,21,25 The regimens evaluated in the meta-analysis were those with dosages of enoxaparin that were documented as effective and approved by the regulatory agencies for clinical use in the countries in Europe or in the United States or Canada.

Four trials14,17,22,24 identified by the literature search did not meet the a priori criteria for inclusion: 3 trials did not use a double-blind design14,17,22 and 3 trials14,22,24 did not define major bleeding according to reproducible criteria.37

**EFFECTIVENESS**

**Table 1** gives the frequency of DVT for preoperative and postoperative prophylaxis with LMWH for the level 18 trials that met the criteria for analysis. **Table 2** gives the analyses of pooled data demonstrating the frequency of DVT in patients receiving preoperative vs postoperative prophylaxis with LMWH.

**SAFETY**

Table 1 gives the frequency of bleeding in the trials that met the criteria for analysis. Table 2 gives the analyses of pooled data demonstrating the frequency of bleeding in patients receiving preoperatively initiated vs postoperatively initiated DVT prophylaxis with LMWH.

**METHODOLOGICAL CONSIDERATIONS**

**Table 3** gives the incidence of DVT for level 1 trials that did not meet the criteria for inclusion. Three trials were not double blind.14,17,22 and 3 trials did not use reproducible criteria for major and minor bleeding.14,22,24

Patient characteristics that were reported in all trials included age, sex, the duration of prophylaxis, and the interval from operation to venography (Table 4). Our findings cannot be explained by differences in these characteristics.
The patient characteristics that resulted in the exclusion of patients from the trials that we included in the meta-analysis were as follows: women with childbearing potential; history of DVT, pulmonary embolism, or both; history of heparin-associated thrombocytopenia; allergy to heparin, LMWH, iodine, protamine sulfate, or radiopaque dye; eye, spinal cord, or nervous system surgery during the last 3 months; younger than 40 years; history of hepatic or renal disease; history of DVT, pulmonary embolism, or cancer. By contrast, 5 of the 6 trials included in our meta-analysis excluded patients with a history of venous thromboembolism, and 5 did not include patients with cancer.

Our findings by meta-analysis support the European view that optimal protection against surgically induced venous thrombosis is provided by preoperatively initiated DVT prophylaxis. The regimen of preoperatively initiated prophylaxis with LMWH was associated with a frequency of DVT of 10.0% compared with 15.3% for postoperatively initiated prophylaxis with LMWH (P = .02). Surprisingly, there was no increased risk of bleeding with the US and Canadian practices. The frequency of major bleeding was, in fact, less for the group receiving preoperatively initiated LMWH than for the group receiving postoperatively initiated LMWH (0.9% vs 3.5%; P = .01).

Our findings show the importance of the recommendation in the International Consensus Statement that “a randomised comparison of the merits of the preoperative and postoperative commencement of pharmacological prophylaxis is necessary.” This recommendation appears under the “Key Questions to Be Answered” section of the article.

Because the comparisons provided by our meta-analysis are across trials rather than direct randomized comparisons, the results may reflect other relevant clinical variables that may have affected the observed outcomes. Adequate data across the trials were reported for age, sex, duration of prophylaxis, and the interval between the operation and venography. The outcomes observed cannot be attributed to differences in the reported values in the key variables (Table 4). Comorbid factors were not consistently reported, and, thus, differences in comorbidity may have influenced the observed outcomes. Variations in the centers in which the trials were conducted and differences in clinical practice also may have contributed to the observed outcomes. For these reasons, the findings are hypothesis-forming and, without further study, should not be used to determine the care of patients.

Table 3. Trials Ineligible for Analysis for Methodological Reasons

<table>
<thead>
<tr>
<th>Trial and Year</th>
<th>All</th>
<th>Proximal Calf Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative low-molecular-weight heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danish Enoxaparin Study Group,15 1991 (n = 108)</td>
<td>7 (6.5)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Planes et al,16 1991 (n = 62)</td>
<td>4 (6)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Eriksson et al,16 1997 (n = 768)</td>
<td>196 (25.5)</td>
<td>59 (7.7)</td>
</tr>
<tr>
<td>Postoperative low-molecular-weight heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planes et al,17 1991 (n = 65)</td>
<td>11 (17)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Colwell et al,18 1994 (n = 272)</td>
<td>36 (13.2)</td>
<td>12 (4.4)</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage). See the “Materials and Methods” section for the criteria for inclusion of trials in the meta-analysis.

Table 4. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preoperative Prophylaxis (n = 124)</th>
<th>Postoperative Prophylaxis (n = 875)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>65.4 ± 9.1</td>
<td>65.8 ± 10.4</td>
</tr>
<tr>
<td>Sex, M/F, No. (%)</td>
<td>61 (49):63 (51)†</td>
<td>482 (55):393 (45)†</td>
</tr>
<tr>
<td>Mean duration of prophylaxis, d</td>
<td>12.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Mean interval, operation to venography, d</td>
<td>12.1</td>
<td>9.6</td>
</tr>
</tbody>
</table>

* These 4 characteristics were reported in all articles included in the meta-analysis.
† P < .001, Fisher exact test.

Our findings may have contributed to the observed outcomes. Variations in the centers in which the trials were conducted and differences in clinical practice also may have contributed to the observed outcomes. For these reasons, the findings are hypothesis-forming and, without further study, should not be used to determine the care of patients.

RELATION BETWEEN TIMING OF PROPHYLAXIS, DOSAGE, AND CLINICAL OUTCOMES

Table 1 gives the relation between the time of initiation of prophylaxis with LMWH, the dosage of LMWH, and the frequency of DVT.

Table 2 gives the relation between the time of initiation of DVT prophylaxis with LMWH, the dosage of LMWH, and the frequency of hemorrhagic complications. The different dosages of LMWH did not alter the preoperative vs postoperative findings.

COMMENT

Our findings by meta-analysis support the European view that optimal protection against surgically induced venous thrombosis is provided by preoperatively initiated DVT prophylaxis. The regimen of preoperatively initiated prophylaxis with LMWH was associated with a frequency of DVT of 10.0% compared with 15.3% for postoperatively initiated prophylaxis with LMWH (P = .02). Surprisingly, there was no increased risk of bleeding with the US and Canadian practices. The frequency of major bleeding was, in fact, less for the group receiving preoperatively initiated LMWH than for the group receiving postoperatively initiated LMWH (0.9% vs 3.5%; P = .01).

Our findings show the importance of the recommendation in the International Consensus Statement that “a randomised comparison of the merits of the preoperative and postoperative commencement of pharmacological prophylaxis is necessary.” This recommendation appears under the “Key Questions to Be Answered” section of the article.

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A trial, which did not meet the eligibility criteria for inclusion in the present meta-analysis, demonstrated a statistically lower frequency of calf-vein thrombosis documented by venography in patients randomized to preoperative initiation of DVT prophylaxis with LMWH compared with patients randomized to postoperative initiation of LMWH prophylaxis. This discrete trial finding supports the findings by meta-analysis.

The findings of the present meta-analysis support the concept that preoperatively initiated DVT prophylaxis for patients undergoing total hip replacement decreases postoperative thrombosis rates without increasing bleeding rates compared with postoperatively initiated DVT prophylaxis. Because our findings are based on a meta-analysis, the reader is cautioned to consider the findings as hypothesis-forming. The relative efficacy and safety of preoperative vs postoperative initiation of prophylaxis can be determined only by comparing these 2 approaches within the same clinical trial.

Accepted for publication April 20, 1998.

We are indebted to Jennifer White, BSc, Victoria Stagg, Andrew Mah, BSc, and Jeanne Sheldon, BA, for their assistance.

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REFERENCES