Recurrent Venous Thrombosis and Heparin Therapy

An Evaluation of the Importance of Early Activated Partial Thromboplastin Times

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Background: The presence of an association between early subtherapeutic activated partial thromboplastin times (aPTTs) and recurrent venous thromboembolism (VTE) remains controversial.

Objective: To determine the relation between early subtherapeutic aPTTs and recurrent VTE in patients who were treated with intravenous (IV) unfractionated heparin (UFH).

Patients and Methods: We studied 961 patients with acute VTE who received IV UFH in 3 randomized trials that compared the use of IV UFH (loading dose: 5000 U IV; initial infusion, 1250-1280 U/h) with that of subcutaneous low-molecular-weight heparin. According to aPTT criteria, patients were classified as being in a subtherapeutic or a therapeutic state during the first 24 and 48 hours of treatment. All episodes of possible recurrent VTE were adjudicated by an independent committee that was unaware of the aPTTs.

Results: At 24 hours, in 886 patients who were eligible for the analysis, the rate of recurrent VTE in the subtherapeutic group was 6.7% (11/163) compared with 5.3% (38/723) in the therapeutic group. The odds ratio for recurrence in patients in the subtherapeutic vs the therapeutic group at 24 hours was 1.30 (95% confidence interval: 0.64-2.63; \( P = .46 \)). At 48 hours, in 917 patients who were eligible for the analysis, the rate of recurrent VTE in the subtherapeutic group was 7.8% (5/64) compared with 5.7% (49/853) in the therapeutic group. The odds ratio for recurrence in patients in the subtherapeutic vs the therapeutic group at 48 hours was 1.32 (95% confidence interval: 0.51-3.44; \( P = .56 \)).

Conclusion: In patients with acute VTE who receive an IV bolus of 5000 U, followed by a starting dose of at least 1250 U/h of UFH, a subtherapeutic aPTT response during the first 48 hours of treatment is not associated with a large increase in the risk of recurrent VTE.

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PATIENTS AND METHODS

Before the completion of the 3 randomized trials, the substudy protocol was formalized. Each trial compared the use of a low-molecular-weight heparin preparation with that of continuous IV UFH for the treatment of acute VTE. In each of the studies, patients were treated with a starting dose of IV UFH consisting of a bolus of 5000 U, followed by a continuous IV infusion of 1250 U/h or 1280 U/h. The aPTTs were obtained 6 hours after starting UFH therapy and then at least every 24 hours, according to standardized nomograms, and the dose of UFH was adjusted to target the specified therapeutic range.

PATIENTS

All patients who were randomly allocated to receive IV UFH were potentially eligible. Patients were classified as subtherapeutic if all aPTTs during the initial 24 or 48 hours were below the lower limit of the therapeutic range. Patients were classified as therapeutic during the 24 hours and the 48 hours after the initiation of IV UFH therapy if any of their aPTTs exceeded the lower limit of the therapeutic range used in each study. In the study by the Columbus investigators, the therapeutic range was defined by an aPTT of 60 to 85 seconds or a fixed aPTT ratio of 1.5 to 2.5 times control values. In the Enoxaparin Treatment Study, the therapeutic range was defined by an aPTT of 60 to 85 seconds. In the Tasman Study, the therapeutic range was defined as being 1.3 to 2.0 times the mean value of the aPTT in normal subjects, which corresponded to an anti-Xa heparin level of 0.35 to 0.60 U/L. Patients were excluded if they were randomly assigned to but did not receive UFH, did not have a clearly defined time of the initiation of UFH therapy and then at least every 24 hours, according to standardized nomograms, and the dose of UFH was adjusted to target the specified therapeutic range.

ANALYSIS AND STATISTICS

The primary outcome measure was objectively confirmed symptomatic recurrent VTE during the 3 months after randomization. All possible recurrences within each of the 3 studies were adjudicated by an independent committee that was unaware of the aPTT results. In the primary analysis, the frequency of recurrent VTE was compared between patients who were classified as therapeutic and those who were classified as subtherapeutic for both the 24- and the 48-hour intervals. Pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel technique. The OR is the ratio of the odds of patients with recurrent VTE within 3 months being subtherapeutic as opposed to being therapeutic in the first 24 or 48 hours. The ORs were considered to be statistically significant if their 95% CI did not include 1.00.

RESULTS

The baseline characteristics of all eligible patients are shown in Table 1. The reasons why randomly allocated patients were excluded from the analysis are shown in Table 2. Overall, 886 patients were included in the analysis at 24 hours and 917 at 48 hours. The rate of recurrence in patients classified as subtherapeutic at 24 hours was 6.7% (11/163) vs 5.3% (38/723) in the patients in the therapeutic group (OR = 1.30, 95% CI: 0.64-2.63; P = .46). The rate of recurrence in the subtherapeutic group at 48 hours was 7.8% (5/64) vs 5.7% (49/853) in the patients in the therapeutic group (OR = 1.32, 95% CI: 0.51-3.44; P = .56) (Table 3).

The importance of achieving a therapeutic aPTT early in the course of IV UFH therapy in patients with VTE is con-
Table 3. Three-Month Recurrence Rates of Symptomatic VTE in Patients by aPTT Classification*

<table>
<thead>
<tr>
<th>Time</th>
<th>Subtherapeutic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Columbus study10</td>
<td>4/76</td>
<td>19/399</td>
</tr>
<tr>
<td>Enoxaparin study12</td>
<td>5/68</td>
<td>10/178</td>
</tr>
<tr>
<td>Tasman study11</td>
<td>2/19</td>
<td>9/146</td>
</tr>
<tr>
<td>Overall</td>
<td>11/163</td>
<td>38/723</td>
</tr>
<tr>
<td>At 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Columbus study10</td>
<td>2/24</td>
<td>22/463</td>
</tr>
<tr>
<td>Enoxaparin study12</td>
<td>2/29</td>
<td>15/224</td>
</tr>
<tr>
<td>Tasman study11</td>
<td>1/11</td>
<td>12/166</td>
</tr>
<tr>
<td>Overall</td>
<td>5/64</td>
<td>49/853</td>
</tr>
</tbody>
</table>

*VTE indicates venous thromboembolism; aPTT, activated partial thromboplastin time.

The results of 2 previous reports5,8 suggested that patients with subtherapeutic aPTTs within the first 24 to 48 hours of the initiation of heparin therapy had a markedly increased risk of recurrence. In contrast, in a meta-analysis7 of 5 randomized controlled trials in which the recurrence rates during the 3-month follow-up period were compared, a pooled OR of 0.89 (95% CI: 0.2-4.0) was obtained for recurrent VTE in association with subtherapeutic aPTTs in the first 48 hours. To help resolve this controversy, we performed a meta-analysis using individual patient data from 3 large randomized trials10-12 that have been completed since the previous meta-analysis. This analysis confirmed that the risk of recurrent VTE was not dramatically increased in patients with subtherapeutic aPTTs at 24 and 48 hours who receive an appropriate starting dose of IV UFH (ie, a bolus of 5000 U followed by an initial infusion of approximately 1250 U/h).

Combining the results of our analysis with those of the previous meta-analysis of the 5 trials produces an OR that is close to 1.00 (1.17) and increases the precision of this estimate by decreasing the range of the 95% CI (0.52-2.62). These data contrast with those of another analysis6 that found an association between an initial subtherapeutic aPTT response and subsequent recurrent VTE in patients treated with IV UFH (OR for recurrence = 5.5, 95% CI: 1.91-15.88). The latter, however, was a retrospective subgroup analysis of relatively few patients, and the method of classifying patients as being subtherapeutic or therapeutic was not clear. Although our study is also a subgroup analysis of 3 trials, the hypotheses and analyses were stipulated a priori, and the potential for bias was further minimized by having all possible recurrences adjudicated by an independent committee that was unaware of the aPTTs.

Our results suggest that, in patients who are treated with appropriate doses of IV UFH, the aPTT response in the first 24 to 48 hours is not an important predictor of recurrent VTE. We cannot, however, conclude that aPTT monitoring has no value because it might be a predictor of bleeding, and it is possible that prolonged (>48 hours) subtherapeutic aPTTs are, indeed, predictive of recurrence. Therefore, in patients with VTE treated with IV UFH, we recommend a 5000-U bolus of UFH, followed by a starting infusion rate of 30 000 to 35 000 U per 24 hours or, alternatively, the use of a weight-adjusted bolus and starting infusion.4 Until shown otherwise, best efforts should be made to achieve therapeutic aPTTs in a timely manner.

CONCLUSIONS

The results of this subgroup analysis of 3 large, randomized controlled trials are consistent with those of a previously published meta-analysis2 in venous thrombosis and a current analysis involving patients with arterial thrombosis (S.S.A, J. Pogue, J.S.G., S. Yusuf, unpublished data, 1998). They demonstrate that in patients who receive a 5000-U bolus of UFH, followed by a starting infusion of 30 000 to 35 000 U per 24 hours, the efficacy of UFH is not critically dependent on early aPTTs.

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