Two Trials of Reduced Bolus Alteplase in the Treatment of Pulmonary Embolism*

An Overview

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The Bolus Alteplase Pulmonary Embolism (BAPE) Group and a consortium of French investigators utilized essentially the same investigational protocol to test reduced dose bolus alteplase vs full dose 100 mg/2 h alteplase in the treatment of pulmonary embolism (PE). The principal hypothesis was that reduced dose bolus alteplase (n = 96) would result in fewer bleeding complications than full dose 100 mg of 2 h alteplase (n = 44) administered as a continuous infusion to hemodynamically stable patients with PE. To provide data on bolus alteplase’s safety profile in a larger sample size than would have been feasible in either trial alone, we present an overview of the BAPE and French trials. There were no differences between the reduced dose bolus and full dose 2 h rt-PA groups with respect to bleeding complications. Therefore, the principal hypothesis of these two randomized controlled trials could not be confirmed. Efficacy was similar in the two treatment groups. Interpretation of the results will vary because the increased convenience and cost savings from using a reduced dose of bolus alteplase may be offset by a higher mortality rate. However, a trial that compared the mortality rates of the two treatment regimens would have required more than 800 patients.

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BAPE=Bolus Alteplase Pulmonary Embolism; PE=pulmonary embolism; rt-PA=recombinant human tissue-type plasminogen activator

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dose bolus vs 100 mg/2 h. They chose to collaborate directly with their BAPE counterparts so that the French trial would be identical to BAPE with respect to treatment regimens, patient allocation ratio, and definitions of major and other important bleeding. This approach was intended to provide an overview of the safety profile of bolus rt-PA in a larger sample size than would have been feasible in either trial alone. We now present the results of the overview of the two trials.

METHODS

Detailed descriptions of the BAPE and French trials are published in this issue of Chest (see pages 712-24). Inclusion criteria for the BAPE trial did not require pulmonary angiography at echocardiography centers. Unilateral angiograms were generally performed at angiography centers, which sought patients with PE in multiple subsegments or in at least one segmental, lobar, or main pulmonary artery. In the French trial, however, bilateral pulmonary angiography was always undertaken to meet the inclusion criterion of PE involving at least half of the pulmonary arterial vasculature. Exclusion criteria and procedures for drug administration were identical in both trials, as were the patient allocation ratio (2:1 ratio for bolus to 2-h rt-PA infusions) and the definition of major and other important bleeding.

“Major bleeding” was defined as (1) any intracranial bleeding, (2) a more than 15-point drop in hematocrit due to any cause (within 72 h of initiating rt-PA) compared with pretreatment, or (3) any bleeding complication that caused death. “Important other bleeding” was defined as gross hematuria, hematemesis, melena, coffee-ground emesis that was heme-positive, or retroperitoneal bleeding—all regardless of change in hematocrit—

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RESULTS

There were no differences between the reduced dose bolus and the full dose 2-h rt-PA groups with respect to safety factors. The rates of all major adverse events were similar in the two groups (Table 1). Although the rate of major or other important bleeding appeared to be almost twice as high in 2-h rt-PA-treated patients, the difference did not approach statistical significance (p=0.19). If the same trend had continued in the overview of the two trials, almost 300 patients (using the same 2:1 allocation ratio) would have been needed to demonstrate a significantly lower bleeding rate in the bolus rt-PA group. This potential advantage in safety would have to be considered carefully because of the possibility of higher mortality in the bolus group, a hypothesis which would have required more than 800 patients to confirm.

With respect to efficacy, perfusion lung scans were obtained in both trials at baseline and at 24 h. Although they were scored according to different methods, both trials found no difference in the absolute improvement in the perfusion lung scan score between the two treatment groups. The magnitude of scintigraphic improvement was similar in both trials: 9 to 11 percent in the BAPE trial and 13 to 14 percent in the French trial. Furthermore, the magnitude of hemodynamic improvement was similar in both groups in the French trial.

DISCUSSION

This overview of two trials of reduced dose bolus vs full dose rt-PA in the treatment of PE shows no significant difference between the two groups with respect to bleeding complications and other major adverse events. Clinically important bleeding complications were observed with bolus rt-PA in both trials, indicating that serious bleeding can occur even though plasma fibrinogenolysis is minimized (BAPE). In terms of clinical, hemodynamic, and imaging endpoints, no differences were observed between treatment groups in either trial.

This combined analysis is important because two groups of investigators obtained remarkably similar results using a shared protocol. The findings in the overview, therefore, strengthen the conclusions of each of the individual trials. In an era of limited re-search funds, this type of collaboration should be encouraged in the planning of future trials.

Interpretation of the results will vary. One approach is to infer that bolus rt-PA should ordinarily be used because it is easier to administer and less expensive. An alternative inference is that, under ordinary circumstances, one should continue to use primarily the Food and Drug Administration-approved 2-h rt-PA regimen because of its nonsignificant trend toward improved efficacy and reduced mortality.

REFERENCES


Table 1—Percent of Major Adverse Events in the BAPE and French (Pulmonary Embolism) Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>Combined Bolus (n=96), %</th>
<th>Combined 2-h Regimen (n=44), %</th>
<th>Probability Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths</td>
<td>5</td>
<td>2</td>
<td>0.67</td>
</tr>
<tr>
<td>Deaths due to bleeding</td>
<td>2</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Deaths due to recurrent PE</td>
<td>3</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>All recurrent PE</td>
<td>7</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding, nonfatal intracranial hemorrhage</td>
<td>5, 0</td>
<td>7, 5</td>
<td>0.71</td>
</tr>
<tr>
<td>Other important bleeding</td>
<td>6</td>
<td>14</td>
<td>0.19</td>
</tr>
<tr>
<td>Major or other important bleeding</td>
<td>11</td>
<td>20</td>
<td>0.19</td>
</tr>
<tr>
<td>Recurrent PE or major or other important bleeding</td>
<td>17</td>
<td>25</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*The probability values are calculated using Fisher’s exact test and refer to the comparison between the combined reduced bolus rt-PA and 100 mg/2 h vs treatment groups.

Overview of Two Reduced Bolus Alteplase Trials (Goldhaber, Feldstein, Sors)