The Uncertain Role of Thrombolytic Therapy in the Treatment of Pulmonary Embolism

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The article by Agnelli et al in this issue of the ARCHIVES presents a clinical outcome–based meta-analysis of thrombolysis vs heparin in the treatment of pulmonary embolism. The authors conclude that a composite end point of death/recurrent PE is lower with thrombolysis than with heparin treatment. Their conclusion is in sharp contrast to a similar review published in the ARCHIVES in 1997 by Dalen et al, who found no evidence that thrombolytic therapy decreases the mortality or the rate of recurrence of PE. The difference in the conclusions of these 2 reports, just 5 years apart, is not due to new data. No new randomized clinical trials of thrombolysis vs heparin in the treatment of PE have been reported since 1995.

Both reports reviewed the same 4 randomized clinical trials that compared recombinant tissue-type plasminogen activator with heparin. Both included the Urokinase Pulmonary Embolism Trial (UPET), which compared heparin and urokinase. The review by Agnelli et al included the UPET and also included 4 other smaller trials of streptokinase or urokinase vs heparin. In these 4 trials, there were 7 deaths among a total of 58 patients treated with heparin, compared with only 1 death among 41 patients treated with streptokinase or urokinase. One of these 4 trials had a major impact on the results. In the study by Jerjes-Sanchez et al, all 4
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Agnelli et al\textsuperscript{6} include recurrent PE in their composite end point. It should be noted that the clinical diagnosis of recurrent PE is less than precise. In the UPET study,\textsuperscript{2} in addition to a lung scan at baseline, scans were repeated 2, 5, and 14 days after treatment. Recurrent PE was suspected in 15 of the 78 patients treated with heparin and 12 of the 82 patients treated with urokinase. However, recurrent PE was confirmed by follow-up lung scan in only 5 heparin-treated patients and 6 urokinase-treated patients. Agnelli et al\textsuperscript{6} report the suspected rate of recurrent PE in the UPET study\textsuperscript{2} in their review. If they had reported the confirmed recurrence rate, the total number of recurrences of PE would have been essentially the same in the 214 patients (3.3%) treated with thrombolytic agents and the 201 (4.5%) treated with heparin.

The many reports and reviews of thrombolytic therapy do agree on several important points:

1. Treatment with the 3 available thrombolytic agents result in earlier resolution of pulmonary embolic obstruction than with heparin. This has been established by angiography,\textsuperscript{2, 10} lung scans,\textsuperscript{2, 8, 9} hemodynamic findings,\textsuperscript{2, 10} and echocardiographic studies.\textsuperscript{8} Unfortunately, the resolution is only partial. In the largest randomized trial, the UPET study,\textsuperscript{2} the percentage of resolution found by lung scan 24 hours after urokinase therapy was 6.2% compared with 2.7% in patients treated with heparin. After 1 week, the percentage of resolution in patients treated with heparin is the same as in patients treated with thrombolytic agents.\textsuperscript{2, 9-11, 16, 17} The much lower degree of resolution of pulmonary emboli with thrombolytic therapy compared with resolution of coronary thrombi in patients with acute myocardial infarction is striking. The difference may be due to the fact that the thrombi in acute myocardial infarction are hours old, whereas pulmonary emboli may have been formed in the veins of the lower extremities days or weeks before thrombolytic therapy.

2. There are significantly more major hemorrhagic complications with thrombolytic therapy than with heparin. In the UPET trial\textsuperscript{2} the incidence of severe bleeding in those treated with urokinase was 27% compared with 13% in those treated with heparin. In a more recent study, Levine\textsuperscript{18} reported an incidence of major hemorrhage
of 8.4% and an incidence of fatal hemorrhage of 2.2% in patients with PE treated with recombinant tissue-type plasminogen activator. Of particular concern is the occurrence of intracranial hemorrhage (ICH) in patients treated for PE with recombinant tissue-type plasminogen activator. In a review by Dalen et al., the incidence of ICH among 559 patients with PE treated with recombinant tissue-type plasminogen activator was 2.1%, and the incidence of fatal ICH was 1.6%. In a report from the International Cooperative Pulmonary Embolism Registry (ICOPER), the incidence of ICH was 3.0% in patients treated with thrombolytic agents compared with 0.3% in patients treated with heparin. The incidence of ICH in patients with PE treated with recombinant tissue-type plasminogen activator is much higher than in patients with acute myocardial infarction treated with the same dose of recombinant tissue-type plasminogen activator.

3. It is clear that the costs of treatment with thrombolytic agents greatly exceed the costs of treatment with heparin.

The central issue is this: in which patients with PE would the benefits of a faster early rate of resolution of embolic obstruction outweigh the increased hemorrhagic risk and the increased cost of thrombolytic therapy? The patients with PE with the highest mortality are those with massive embolism complicated by shock. The mortality in this circumstance is in the range of 30%. The ICOPER report noted a 58% mortality among 96 patients with PE who were hemodynamically unstable at the time of presentation. Fortunately, only a minority of patients with PE present with shock. There have been no randomized clinical trials to compare the results of heparin therapy with thrombolytic therapy or pulmonary embolectomy in patients with massive PE complicated by shock. In the absence of contraindications, it is reasonable to consider thrombolytic therapy in these patients, as recommended by the American College of Chest Physicians Task Force on Antithrombotic Therapy. A randomized clinical trial is needed to determine if thrombolytic therapy benefits this group of patients.

The vast majority of patients with PE are hemodynamically stable at presentation, and their prognosis with heparin therapy followed by treatment with warfarin is very good. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, only 1 of the 399 patients presented with hemodynamic instability, and only 6% of the patients underwent thrombolytic therapy. The total in-hospital mortality due to PE was 2.2%. In a meta-analysis of 5 studies including 1302 patients with PE treated with heparin followed by warfarin, Douketis et al. reported a rate of fatal PE of 1.5% and a rate of fatal and possible fatal cases of PE of 2.3%. Since the rate of fatal hemorrhage with recombinant tissue-type plasminogen activator is 2.2%, it is clear that thrombolytic therapy is not the appropriate therapy for patients with PE who are hemodynamically
Is there a subset of patients with PE who, even though hemodynamically stable, are at such a high risk of death as to warrant thrombolytic therapy? This question is at the core of the uncertainty about the role of thrombolytic therapy. Cannon and Goldhaber have recommended that patients with PE who are hemodynamically stable should be treated with thrombolytic agents if they have echocardiographic evidence of right ventricular dysfunction (RVD). Since 40% to 50% of patients with acute PE have echocardiographic evidence of RVD, this recommendation would greatly increase the number of patients with PE treated with thrombolytic agents. There have been no reports of randomized trials comparing thrombolysis with heparin therapy in hemodynamically stable patients with PE and echocardiographic evidence of RVD. We agree with Agnelli et al and many others that such a trial is urgently needed. Until such a trial is reported, should hemodynamically stable patients with RVD be treated with heparin or thrombolysis?

The primary evidence favoring thrombolytic therapy derives from the report by Konstantinides et al from a multicenter registry in Germany. During 1993 and 1994, 1001 patients with a diagnosis of PE were seen at 204 participating centers. A total of 719 patients were hemodynamically stable at presentation. The 30-day mortality among 172 hemodynamically stable patients who did not have RVD was 4.1% compared with 10% among 380 patients with RVD. The mortality in these patients without shock is higher than in subsequent reports. As shown in Table 1, the mortality among 216 patients without RVD or shock in 3 reports was 0.9% compared with 4.0% in 167 patients with RVD. In the report from the German registry, the choice of therapy was determined by the individual investigators at each of the 204 centers. A total of 169 (24%) of the patients were treated with thrombolytic agents, and 76% were treated with heparin. The 30-day mortality was 4.7% in the thrombolytic group and 11.1% in the heparin group (P = .02). The data from this large registry are very important, but since therapy was at the discretion of each investigator, selection bias could have influenced the results. Arasoy and Kreit in their review point out that the patients selected for thrombolytic therapy were younger and much less likely to have associated cardiac or pulmonary disease than the patients treated with heparin.

The results from another registry, this one in France, were quite different than the results from the multicenter registry in Germany. Hamel et al report that 153 consecutive patients with massive PE were treated with thrombolysis (n = 80) or heparin (n = 73), depending on the decision of the attending physician. To study comparable patients, 64 patients treated with heparin were matched on baseline echocardiographic right ventricular–left ventricular diastolic diameter ratio to 64 patients treated with thrombolysis. The 2 groups were evenly matched; there was no significant difference in age, presence of associated cardiac or pulmonary disease, or the
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The magnitude of defect by lung scan. The results, as listed in Table 2, were striking. There were no deaths in the patients treated with heparin vs a 6.25% mortality in those treated with thrombolysis. The rate of recurrent PE was the same in both groups. Severe bleeding occurred in 9.4%, and ICH occurred in 4.7% of patients treated with thrombolysis. There was no severe bleeding or ICH in the patients treated with heparin.

As pointed out by Davidson and Lensing, Goldhaber et al. and Konstantinides et al. support the argument that more patients with PE should be treated with thrombolysis. However, Hamel et al suggest that if more patients with PE were treated with thrombolysis, additional intracranial bleeding events and additional deaths would occur. Until the results of a randomized trial become available, I believe that thrombolytic therapy should only be considered in patients with massive PE complicated by shock.

Author/Article Information

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