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Thrombolytic Therapy for Acute Pulmonary Embolism: When do the Benefits Exceed the Risks?

Thrombolytic agents lyse venous thromboemboli more rapidly than treatment with heparin and the natural thrombolytic processes.[1-4] Thrombolytic therapy for acute pulmonary embolism, irrespective of the agent used, also is associated with major bleeding.[5] The most devastating complication of thrombolytic therapy is intracranial hemorrhage. Pooled data in 559 patients showed intracranial hemorrhage in 2.1% treated with recombinant tissue plasminogen activator.[6] Intracranial hemorrhages were fatal in 76%.[6]

WHEN IS THROMBOLYTIC THERAPY INDICATED FOR ACUTE PULMONARY EMBOLISM?

The first randomized controlled trial, the Urokinase Pulmonary Embolism Trial in 1973, showed no difference in mortality among 82 pulmonary embolism patients who received urokinase and 78 who received heparin.[1] Subsequent randomized trials also showed that in normotensive patients not stated to have right ventricular dysfunction, the mortality with thrombolytic therapy was comparable to the mortality with heparin, irrespective of the type of thrombolytic agent used.[2,4,7,8] There is no evidence that thrombolytic therapy decreases the mortality of acute pulmonary embolism in patients who are not in shock and not stated to have right ventricular dysfunction.

THROMBOLYTIC THERAPY IN PATIENTS WITH PULMONARY EMBOLISM AND SHOCK

In the Urokinase Pulmonary Embolism Trial, only 14 of 160 patients (9%) were in shock.[1] Among these, 8 received urokinase and 4 received heparin. All lived. Jerjes-Sanchez et al,[9] in a randomized controlled trial of patients with pulmonary embolism who were in cardiogenic shock, showed survival in 4 of 4 (100%) with streptokinase and 0 of 4 (0%) with heparin ($P = .02$). Data from the Nationwide Inpatient Sample among 72,230 unstable patients with pulmonary embolism, showed 15% all-cause mortality with thrombolytic therapy vs 47% with anticoagulants.[10] In the 9th edition of the *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines* (2012),[11] thrombolytic therapy was recommended for hypotensive patients with pulmonary embolism. It is unlikely that a randomized controlled trial in patients in shock will be performed to prove the value of thrombolytic therapy.

ARE THERE OTHER INDICATIONS FOR THROMBOLYTIC THERAPY?

Right ventricular dysfunction (right ventricular enlargement or paradoxical septal motion) in normotensive patients with pulmonary embolism has been classified as "impending hemodynamic instability."[12] A higher mortality has been reported among such patients.[13]

MORTALITY WITH LYTICS AND RIGHT VENTRICULAR DYSFUNCTION, BUT NO SHOCK

A registry of normotensive patients with right ventricular dysfunction showed an all-cause mortality of 8 of 169 (4.7%) with thrombolytic therapy, vs 61 of 550 (11.1%) with anticoagulants ($P = .016$).[14] One randomized trial of such patients also showed a lower all-cause mortality with thrombolytic therapy, 0 of 37 (0%) vs 6 of 35 (17%) with heparin ($P = .01$).[15] However, several randomized trials[3,16-20] and a registry[21] failed to show a lower mortality with thrombolytic therapy in normotensive patients with right ventricular dysfunction.

Chatterjee et al[22] reported a meta-analysis of 16 randomized trials of thrombolytic vs anticoagulant therapy for patients with acute pulmonary embolism. Eight of the randomized trials reported by Chatterjee et al[22] were in "intermediate-risk" patients. In 7 of these trials, patients were normotensive with right ventricular dysfunction.[22] In one trial, patients had moderate-risk pulmonary embolism-based appearance of the images.[23] Mortality with thrombolytics in

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Requests for reprints should be addressed to Paul D. Stein, MD, Michigan State University, College of Osteopathic Medicine, Detroit Medical Center, 4707 St Antoine - Box 402, Detroit, MI 48201.

E-mail address: steinp@msu.edu

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intermediate-risk patients with right ventricular dysfunction was 12 of 866 (1.4%), vs 26 of 889 (2.9%) with anticoagulants ($P = .03$).[22] Major bleeding occurred in 7.7% with thrombolytics, vs 2.3% with anticoagulants ($P < .001$).[22]

The largest randomized trial of normotensive patients with right ventricular dysfunction was in patients who also had a positive test for troponin I or T.[17] All-cause mortality with thrombolytics (tenecteplase) was 6 of 506 (1.2%), vs 9 of 499 (1.8%) with anticoagulants ($P = .42$).[17] Major bleeding was 58 (11.5%) with thrombolytics vs 12 (2.4%) with anticoagulants.[17] Hemorrhagic stroke was 10 (2.0%) with thrombolytics vs 1 (0.2%) with anticoagulants. Hemodynamic decompensation was less frequent with thrombolytics, 8 (1.6%) vs 25 (5.0%) with anticoagulants ($P = .002$).[17] In our opinion, the increased risk of hemorrhagic complications exceeded any benefits.

CONCLUSIONS

After more than 40 years of controversy, we conclude that the only indication for thrombolytic therapy in patients with acute pulmonary embolism continues to be the presence of shock.

Paul D. Stein, MD[a]
James E. Dalen, MD, MPH[b]
[a]*Professor*
Osteopathic Medical Specialties
Michigan State University College of Osteopathic Medicine
Detroit
[b]*Dean Emeritus and Professor Emeritus*
University of Arizona College of Medicine
Tucson

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