Neuroanesthesia and Intensive Care

Best evidence in critical care medicine

Treatment of submassive pulmonary embolism

Article appraised

Konstantinides S, Geibel A, Hensel G, Heinrich F, Kasper W; for the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002; 347: 1143–50.

Structured abstract

Background: Thrombolysis is considered to be standard therapy for patients with pulmonary embolism presenting with shock, despite a paucity of large clinical trials. The benefit of thrombolysis in submassive pulmonary embolism (right ventricular dysfunction without shock) is debated.

Question: Is anticoagulation plus thrombolytic therapy more effective than anticoagulation alone for submassive pulmonary embolism?

Design: Prospective, randomized, double-blind, placebo-controlled trial in 49 German medical centres.

Patients: Two hundred fifty-six normotensive patients (48% male, mean age 62 yr) with proven acute pulmonary embolism and echocardiographic, electrocardiographic or pulmonary artery catheter evidence of right ventricular dysfunction were randomized within 96 hr of presentation. Baseline characteristics were similar save for an excess number of patients with the S₁Q₃ electrocardiographic pattern in the anticoagulation arm.

Intervention: Patients received 5,000 U unfractionated heparin *iv* prior to diagnostic workup, followed by alteplase 10 mg *iv* bolus and 90 mg *iv* over two hours or matching placebo. Heparin was started in all patients at 1,000 U·hr⁻¹, and titrated to activated partial prothrombin time of two to 2.5 times the upper limit of normal.

Primary end-point: Combined in-hospital mortality or clinical deterioration requiring escalation of treatment (catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or embolectomy/thrombus fragmentation).

Results: Thrombolysis reduced the primary end-point by 13.7% ($P = 0.006$, number-needed-to-treat ~ 7), driven by reduction in the need for secondary thrombolysis. There was no mortality benefit (3.4% *vs* 2.2%, $P = 0.71$) or difference in complications and only one fatal bleeding episode (in the anticoagulation arm). Adequacy of anticoagulation was equivalent by 12 hr.

Conclusion: The addition of alteplase to heparin therapy for submassive pulmonary embolism does not reduce mortality, but does reduce the need for escalation of treatment due to clinical deterioration.

Commentary by R. C. McDermid

There is great interest in thrombolysis for pulmonary embolism with submassive pulmonary embolism due to the association of right ventricular dysfunction and increased mortality.¹ The data from Konstantinides *et al.* indicate that early administration of alteplase is safe and reduces the need for rescue thrombolysis, although mortality is unchanged. The study definition of right ventricular dysfunction was very broad, including echocardiographic (only 31% of patients), pulmonary artery catheter and electrocardiographic criteria.

Right ventricular function appears to improve more rapidly in patients receiving thrombolysis, although this benefit does not persist beyond 72 hr.² No studies have shown an improvement in embolic burden lasting beyond the first week.³ Thus, the primary benefit of thrombolysis is rapid reduction in right ventricular work and improvement in cardiac output, an effect that may be most important in those patients who have myocardial damage or inadequate tissue perfusion. A recent study has shown that troponin I has prognostic value and is closely linked to echocardiographic evidence of right ventricular dysfunction.⁴

Although thrombolysis seems intuitively appropriate for patients with pulmonary embolism and right ventricular dysfunction, the data are not entirely convincing unless it is also accompanied by shock. Close monitoring and immediate thrombolysis when shock

develops is an alternative. Further study of thrombolysis for severe subsets of pulmonary embolism is warranted.

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References

- 1 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353: 1386–9.
- 2 Vicillard-Baron A, Page B, Augarde R, et al. Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. *Intensive Care Med* 2001; 27: 1481–6.
- 3 Wood KE. The presence of shock defines the threshold to initiate thrombolytic therapy in patients with pulmonary embolism. *Intensive Care Med* 2002; 28: 1537–46.
- 4 Konstantinides S, Giebel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation* 2002; 106: 1263–8.