Heparin plus alteplase reduced morbidity more than heparin alone in submassive pulmonary embolism

Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. **Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism.** N Engl J Med. 2002;347:1143-50.

QUESTION

Is heparin plus alteplase more effective than heparin alone in patients with acute submassive pulmonary embolism (PE)?

DESIGN

Randomized {allocation concealed*}†, blinded {patients, clinicians, data collectors, outcome assessors, monitoring committee, and data analysts}†,* placebo-controlled trial with follow-up at 30 days (Management Strategies and Prognosis of Pulmonary Embolism-3 Trial).

SETTING

49 centers in Germany.

PATIENTS

256 patients (mean age 62 y, 52% women) with acute PE and right ventricular dysfunction or strain or pulmonary artery hypertension. Exclusion criteria were age > 80 years; hemodynamic instability; symptom onset > 96 hours before diagnosis; thrombolysis, surgery, or biopsy within 7 days; major trauma within 10 days; stroke, transient ischemic attack, head trauma, or neurosurgery within 6 months; gastrointestinal bleeding within 3 months; uncontrolled hypertension; known bleeding disorder; alteplase intolerance; diabetic retinopathy; current oral anticoagulant therapy; pregnancy or lactation; life expectancy < 6 months; or planned use of thrombolysis for deep venous thrombosis. Follow-up was complete.

INTERVENTION

All patients received an intravenous infusion of unfractionated heparin, starting at 1000 U/h and adjusted to maintain the activated partial thromboplastin time at 2.0 to 2.5 times the upper limit of normal and oral anticoagulant therapy starting at day 3, with a target international normalized ratio of 2.5 to 3.5. 118 patients were allocated to alteplase, 100 mg, as a 10-mg bolus, followed by a 90-mg intravenous infusion over 2 hours, and 138 patients were allocated to matching placebo.

MAIN OUTCOME MEASURES

Combined endpoint of in-hospital death and clinical deterioration requiring escalation of treatment. Secondary outcomes included recurrent PE, major bleeding, and ischemic stroke.

MAIN RESULTS

Analysis was by intention to treat. Patients who received alteplase had lower rates of the combined endpoint and clinical deterioration than did those who received placebo (Table). The groups did not differ for all-cause mortality (Table), recurrent PE (P = 0.89), major bleeding (P = 0.29), or ischemic stroke (P = 1.0).

CONCLUSION

Heparin plus alteplase reduced the combined endpoint of in-hospital death and clinical deterioration requiring escalating treatment more than did heparin alone; the groups did not differ for all-cause mortality.

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*See Glossary.

†Information provided by author.

Heparin plus alteplase vs heparin plus placebo for acute submassive pulmonary embolism‡

Outcomes at 30 d	Alteplase	Placebo	RRR (95% CI)	NNT (CI)
Combined endpoint§	11%	25%	55% (21 to 75)	8 (5 to 24)
Clinical deterioration	10%	25%	59% (25 to 78)	7 (5 to 20)
			RRI (CI)	NNH
All-cause mortality	3.4%	2.2%	56% (–60 to 513)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
§In-hospital death or clinical deterioration requiring escalation of treatment.

COMMENTARY

The role of thrombolysis in patients with PE has been an area of long-standing debate. Although thrombolysis is an accepted first-line treatment in patients with massive PE who present with hypotension or shock (1), its role in most patients with hemodynamically stable submassive PE is controversial (2, 3). This is due, in part, to the uncertain prognosis of such patients who receive conventional heparin therapy. The incidence of fatal PE is about 7% in patient registries, whereas it is 1% to 2% in randomized trials (4). In general, thrombolysis for submassive PE has not been widely adopted because of a lack of compelling evidence of superior efficacy over heparin and concerns about a 4-fold higher risk for major bleeding (2).

The study by Konstantinides and colleagues is the largest trial to compare thrombolysis with heparin. It involves patients with submassive PE and right ventricular strain, who would presumably benefit most from rapid clot lysis. Furthermore, the low bleeding rate with thrombolysis provides reassurance of its safety in carefully selected patients. The results suggest the superiority of thrombolysis when endpoints relating to clinical deterioration are considered. However, when conventional endpoints of recurrent PE and mortality are considered, no difference exists between the 2 treatments. The possible benefits of thrombolysis remain to be determined for such outcomes as long-term functional assessment or chronic pulmonary hypertension.

These results, although promising, are not sufficiently compelling to advocate widespread use of thrombolysis in patients with submassive PE. There is a need to identify patient subgroups with PE in whom the benefits of thrombolysis are unequivocal. The debate continues.

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