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Recombinant tissue plasminogen activator for hemodynamically stable patients experiencing an acute pulmonary embolism: A meta-analysis

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ABSTRACT

Background: The role of thrombolytic therapy for the initial treatment of hemodynamically stable patients experiencing an acute pulmonary embolism remains controversial.
Methods and Results: We performed a meta-analysis of randomized trials comparing between administration of recombinant tissue plasminogen activator (rt-PA) and heparin in hemodynamically stable patients experiencing an acute pulmonary embolism. Seven trials, involving 594 patients, were included in this meta-analysis. Compared with heparin, rt-PA was associated with a non-significant reduction in death (2.75% versus 3.96%; RR 0.69, 95% CI 0.31-1.52, P for heterogeneity = 0.520) and recurrent pulmonary embolism (2.13% versus 3.34%; RR 0.70, 95% CI 0.28-1.73), and a non-significant increase in major bleeding (5.15% versus 4.29%; RR 1.06, 95% CI 0.520-2.150). Similar results were found based on a subgroup analysis of patients displaying echocardiographic evidence of right ventricular dysfunction (RVD). In contrast, rt-PA treatment was associated with a significant reduction in escalation of care in trials that also enrolled patients displaying RVD compared with heparin treatment (6.56% versus 19.7%; RR 0.34, 95% CI 0.20-0.65).
Conclusion: The currently available data provide no evidence for a benefit of administration of rt-PA compared with heparin for the initial treatment of hemodynamically stable patients experiencing an acute pulmonary embolism. However, rt-PA is partially beneficial specifically among patients displaying RVD.

Introduction

The prognosis of patients experiencing a pulmonary embolism (PE) correlates to earlier risk stratification and higher mortality in "high-risk" (as defined by the European Society of Cardiology [1]) or "massive" (as defined by the American Heart Association [2]) patients. Patients experiencing a massive or high-risk PE exhibit hemodynamic instability that presents as persistent systemic arterial hypotension and shock [1,2], which may be responsible for the high death rate of massive PE. Thrombolytic therapy may represent a critical strategy to improve the situation. Current American and European guidelines [1,2] for the use of thrombolysis to treat PE focus on high-risk or massive patients. For most hemodynamically stable patients experiencing a PE, systematic thrombolysis is not recommended as an adequate treatment [1]. A previous meta-analysis of randomized trials comparing between administration of recombinant tissue plasminogen activator (rt-PA) and heparin in normotensive patients experiencing a PE revealed no significant benefit of thrombolysis [3]. However, a retrospective study suggested that echocardiographically detected right ventricle dysfunction (RVD) may indicate adverse outcome in normotensive patients [4]. A recent randomized trial indicated that early thrombolysis for normotensive patients displaying RVD could improve the clinical course and prevent clinical deterioration during the hospital visit [5]. In addition, two of the most recent randomized trials comparing thrombolysis with heparin treatment demonstrated a more favorable trend in the clinical outcome of thrombolysis for normotensive patients displaying evidence of RVD [6,7]. To explore the effect of thrombolysis on the outcome of normotensive patients, we performed an updated meta-analysis of randomized trials of thrombolysis compared to anticoagulation for hemodynamically stable patients experiencing an acute PE. For normotensive patients displaying evidence of RVD, which are defined as intermediate-risk or submassive patients [1,2], we performed a subgroup analysis of the clinical outcomes.

Abbreviations: rt-PA, recombinant tissue plasminogen activator; RVD, right ventricular dysfunction; PE, pulmonary embolism; RR, relative risk; CI, confidence interval; CTPA, computed tomography pulmonary angiography; CT, computed tomography; FABPs, fatty acid–binding proteins; PEITHO, pulmonary embolism thrombolysis.

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Methods

Literature search

Relevant randomized clinical trials were identified by searching the electronic databases MEDLINE (from January 1966 to June 2013), Embase (from January 1975 to June 2013), and the Cochrane library (2013, Issue 7). The search terms were: pulmonary embolism, thrombolysis, fibrinolysis, recombinant tissue plasminogen activator, rt-PA, alteplase, tenecteplase, heparin, and randomized controlled trial. Only those trials published containing data accessible in English were searched.

Study Selection

Our primary objective was to evaluate the effect of thrombolysis on clinical outcomes among normotensive patients experiencing an acute PE. We included clinical trials meeting the following criteria in the meta-analysis: 1) prospective randomized trials, 2) patients with a confirmed acute pulmonary embolism who were not experiencing shock or hemodynamic collapse (systolic blood pressure > 90 mmHg), 3) patients treated with rt-PA plus heparin versus heparin alone for the initial treatment of PE, and 4) the clinical outcomes of all-causes death, PE recurrence, and major hemorrhage were reported. Two investigators independently assessed the methodological quality of the studies using the Jadad scale, in which the trials were ranked from 0 to 5 based on trial design elements, such as blinding and randomization [8].

Data extraction and clinical outcomes

Data extraction was independently performed by two investigators on the studies which met the inclusion criteria. Data including the year of publication, the number of participants enrolled, the trial phase, the treatment arms and the efficacy and safety outcomes prior to hospital discharge or within 30 days after the first episode were collected. When disagreement between the two investigators existed, a third investigator helped to extract the data. The efficacy outcomes were measured as death from all causes, death related to PE, PE recurrence and treatment escalation. PE recurrence was taken into account when proven by either radiological assessment or autopsy. Escalation of care was defined as the need for one or more of the following: catecholamine infusion for sustained hypotension or shock, endotracheal intubation, cardiopulmonary resuscitation, emergency surgical embolectomy or catheter fragmentation. The safety outcome was measured as major hemorrhage, which was defined as fatal or pericardial or retroperitoneal or intracranial, requiring transfusions or intervention to treat hemodynamic deterioration according to the definitions of the original studies.

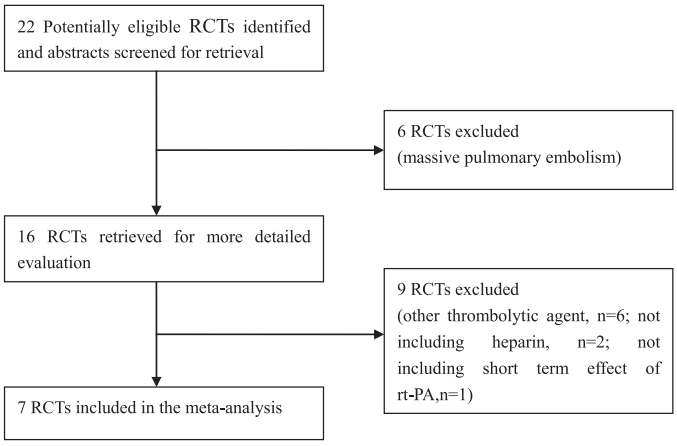
Statistical analysis

The analysis was performed using Stata software version 11.0. The relative risk (RR) and the 95% confidence interval (CI) for thrombolysis plus heparin versus heparin alone were calculated for each endpoint. A subgroup analysis was performed for the studies which included participants displaying echocardiographic evidence of RVD. Heterogeneity of the results of the trials was estimated by performing a Cochran-Q test and the I-squared measure, which represents the variation in the RR that is attributable to heterogeneity. Significant heterogeneity was defined as a chi-squared test revealing $P < 0.1$ [9] or an I-squared value measuring greater than 50% [10]. When the heterogeneity was not significant, we used a fixed effect model to pool the results. The RR and the 95% CI were pooled using the Mantel-Haenszel method. A random-effects model was used when the heterogeneity was significant. We evaluated publication bias using Eegg's test.

Results

Study selection

Our search identified 22 potentially eligible randomized controlled trials. Six trials were excluded because they included patients experiencing acute massive pulmonary thromboembolism [11–16]. Another six studies were excluded because the thrombolytic agent used was not rt-PA [17–22]. Two additional studies were excluded because they compared between different bolus doses of rt-PA rather than between rt-PA and heparin [23,24]. One study was excluded because it did not provided data regarding the short term effect of rt-PA [25]. Ultimately, seven studies were included in this meta-analysis [5–7,26–29]. Study selection process is presented in the flow chart.



Flow chart of study selection process. RCTs indicates randomized, controlled trials.

Study characteristics

The seven included articles were published in 1990–2013, and all of the studies reported the predefined endpoints. Their Jadad scores ranged from one to five, with a median of three. All of the included studies were randomized controlled trials, although only three of them [5,6,29] clearly provided the method of randomization. Five trials [5–7,26,27] were double-blind and one trial [28] was single blind with respect to the evaluation of angiography and lung scan. The sample sizes ranged from 13 to 256. There were no losses in follow-up in four trials, and the number of withdrawals and dropouts was reported in one trial. The methodological quality of the trials is reported in Table 1. For each endpoint, no evidence of publication bias was detected based on Eegg's test (p values ranging from 0.315 to 0.815) and heterogeneity (heterogeneity test $P > 0.1$, I-squared < 50%) (Fig. 1). A total of 594 patients were included in the analysis: 291 received thrombolytic therapy plus heparin, and 303 received only heparin. The patients in five of the studies [5,26–29] were diagnosed based on pulmonary angiography, V/Q scan or computed tomography pulmonary angiography (CTPA), while some patients of two recent articles [6,7] were diagnosed based on lung spiral computed tomography (CT) and positive clinical characteristics. Six trials [5,7,26–29] examined administration of rt-PA plus heparin versus heparin alone for the initial treatment of PE using rt-PA doses ranging from 40 to 100 mg/m^2, while another trial

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