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Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: A meta-analysis

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ABSTRACT

Introduction: The role of thrombolysis in hemodynamically stable patients with acute pulmonary embolism (PE) remains controversial. We performed a meta-analysis of randomized trials to assess the effect of thrombolysis in these patients.
Materials and Methods: We searched MEDLINE and EMBASE for randomized studies comparing thrombolysis and heparin for the initial treatment of hemodynamically stable PE patients. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated. NNH to cause a major bleeding (MB) or an intracranial hemorrhage (ICH) and NNT to avoid one death were also calculated.
Results: Eleven studies (1833 patients) were included seven with rt-PA, three with tenecteplase and one with urokinase. Patients randomized to thrombolysis had a significant increased risk for MB (5.9% vs 1.9%; OR 2.83, 95% CI 1.68-4.76, I^2 18.7%) and an increased risk for ICH (1.74% versus 0.6%; OR 2.36, 95% CI 0.98-5.71, I^2 0%) and for fatal bleeding (1.3% versus 0.54%; OR 1.84, 95% CI 0.73-4.61, I^2 0%). A not-significant reduction for all-cause death (1.74% vs 2.51%; OR 0.68, 95% CI 0.37-1.26, I^2 0%) and a significant reduction for recurrent PE (1.1% vs 2.5%; OR 0.44, 95% CI 0.21-0.92, I^2 0%) in favor of thrombolysis compared with heparin was found. NNH to cause a MB or an ICH were 27 and 91 patients, respectively. NNT to avoid one death was 125 patients.
Conclusions: Due to increased risk for MB and ICH with no evidence of reduction in mortality, thrombolysis should not be used for most normotensive PE patients.

Introduction

Pulmonary embolism (PE) is a common disease associated with a substantial risk for short-term mortality that can be as high as 30% in hemodynamically unstable patients [1]. The clinical management of hemodynamically stable patients with acute PE is an everyday clinical challenge [2]. The wide range of short-term mortality observed in these patients (from 15 to less than 1%) suggests the need for tailoring their clinical management according to the specific risk for death [1,3,4].

Thrombolytic treatment provides a more rapid lysis of pulmonary emboli, reduction of pulmonary hypertension and improvement in right ventricle (RV) dysfunction than heparin [5,6]. A reduction in mortality has been shown with thrombolytic treatment in patients with PE associated with hemodynamic compromise [7]. Whether thrombolytic treatment results in an improved clinical outcome and outweigh the potential increased risk of bleeding complications in hemodynamically stable patient with acute PE remains controversial.

A large randomized placebo controlled trial (PEITHO) aimed at assessing the clinical benefit of thrombolysis in normotensive patients with acute PE, has recently been concluded [8]. In this trial, the clinical benefit of tenecteplase in terms of reduction in mortality and clinical deterioration at 7 days was counterbalanced by a high risk for major bleeding (MB).

We performed a meta-analysis of randomized clinical trials (RCTs) to compare thrombolysis and heparin versus heparin alone in hemodynamically stable patients with acute PE.

Methods

Data sources and searches

We attempted to identify all RCTs which compared thrombolysis and heparin for the initial treatment of acute PE in hemodynamically stable patients by computer aided search (MEDLINE and EMBASE), and scrutiny of the reference lists of original research and review articles. We searched electronic databases MEDLINE and EMBASE using the terms "pulmonary embolism," "thrombolysis", and "thrombolytic therapy," in combination with generic names of individual thrombolytic agents.

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Study selection

Three investigators (C.B., M.G., A.R-M.) independently evaluated studies for inclusion, and any disagreement was resolved by discussion. Criteria for inclusion were: (1) RCTs comparing thrombolysis with heparin for the initial treatment of acute PE, (2) inclusion of patients with objectively diagnosed symptomatic PE, (3) availability of data on death, bleeding and PE recurrence for hemodynamically stable patients.

Data Extraction and quality assessment

Three investigators (C.B., M.G., A.R-M.) independently extracted data on study (year of publication, design), population characteristics (number of patients, mean age), and treatment (type of drug, dose, and duration). Information on the following outcomes was collected in the two groups: number of MB, intracranial hemorrhage (ICH), all-cause death, PE recurrence, fatal PE and fatal bleeding. If outcome data for extraction could not be identified, the study authors were contacted. Disagreements on study data extraction was resolved by consensus or by discussion with a fourth reviewer (G.A.).

Two reviewers (M.G., A.R-M.) independently assessed study quality using the Jadad score based on the following criteria: methods used to generate the randomization sequence, method of double blinding, and description of patient withdrawals and dropouts [9]. A score of 1 point was given for each criterion satisfied, and 1 additional point was given for high quality of randomization and double blinding, for a maximum of 5 points. Studies with a score higher than 2 were considered of high quality, and studies with a score of 2 or lower were considered of low quality.

Outcomes

The primary outcomes of this meta-analysis were MB and ICH, occurring during hospital stay or within 30 days from acute PE. Secondary outcomes were all-cause death, PE recurrence, fatal PE and fatal bleeding during the same studied period.

Due to differences in the definition of major bleeding across the individual studies, we attempted to reclassify these events in accordance to the ISTH and the TIMI definitions [10,11].

Statistical Analysis

The analysis was performed separately for each adverse outcome event (MB, ICH, all-cause death, PE recurrence, fatal PE and fatal bleeding), and for the composite outcome of death or PE recurrence. The results of each trial were analyzed on an intention-to-treat basis. Pooled odds ratios (ORs) were reported with 95% confidence intervals (CIs). Data were pooled by use of a fixed-effects model (Mantel-Haenszel method), and results were compared with the results obtained with a random-effects (RE) model (DerSimonian-Laird method) [12,13]. A continuity correction of 0.5 was applied for studies without event in one arm. A value of P lower than 0.05 was considered statistically significant. Cochran's $\chi 2$ test and the I2 test for heterogeneity were used to assess between-study heterogeneity [14]. Statistically significant heterogeneity was considered present at $P < 0.10$ and $I2 > 50\%$. Publication bias was assessed visually by the use of funnel plots.

Subgroup analyses were performed to explore the treatment effect of different thrombolytic agents. We also analyzed the incidence of the primary outcomes in RCTs using alteplase or tenecteplase compared with heparin, separately.

The number needed to treat (NNT) and the number needed to harm (NNH) were calculated as the inverse of the Absolute Risk Reduction (ARR).

All statistical analyses were performed using STATA version 6.0 statistical software (Stata Corp., College Station, Texas) and Comprehensive Meta Analysis, version 1.0.23 (Biostat; 1998).

Results

Study identification and selection

Our search identified 22 potentially eligible RCTs, of which one was identified by hand-searching [15]. Studies were excluded from the analysis if they compared different thrombolytic agents or different regimens of a single agent (6 studies) or if data on hemodynamically stable patients were not available (5 studies). Eleven studies (1833 patients) were definitely included in the analysis, seven with rt-PA [5,16–21] three with tenecteplase [6,8,22] and one with urokinase [15]. For 2 studies inclusion was made possible after contact with authors for retrieval of unpublished data [21,22]. The flow selection is reported in Fig. S1 in the Online Supplementary Material and the main features of the individual studies are reported in Table 1.

With the use of the Jadad score, 4 studies were classified as low quality and 7 as high quality [9]. All the trials were randomized, but the method to generate the randomization sequence was adequately reported in 6 studies. Seven studies were double-blind. Ten studies provided a description of patient withdrawals. Quality assessment items are summarized in Table S1 in the Online Supplementary Material.

Primary outcomes

Reclassification of MB in accordance to the ISTH and/or to the TIMI definitions was not possible using available data from RCTs. Thus, MB was defined according to the definition used in the individual studies (Table S2 in the Online Supplementary Material).

An increased risk for MB was found in patients randomized to receive thrombolytic agents (5.9% vs 1.9%; OR 2.83, 95% CI 1.68-4.76, I^2 18.7%) (Fig. 1). NNH for major bleeding was 27 patients. Funnel plot inspection showed evidence of publication bias (Online Supplementary Material Fig. S2).

An increase in ICH (1.74% versus 0.6%; OR 2.36, 95% CI 0.98-5.71, I^2 0%) was also found in patients receiving thrombolysis compared to patients receiving heparin alone (Fig. 2). NNH for ICH was 91 patients.

A not significant increased risk for fatal bleeding (1.3% versus 0.54%; OR 1.84, 95% CI 0.73-4.61, I^2 0%) was found in patients receiving thrombolysis (Fig. S3 in the Online Supplementary Material). NNH for fatal bleeding was 143 patients.

Pooled data for safety and efficacy outcomes are shown in Table 2.

Secondary outcomes

A not statistically significant reduction in all-cause death was observed for thrombolysis compared with heparin (1.74% vs 2.51%; OR 0.68, 95% CI 0.37-1.26, I^2 0%) (Fig. 3). The NNT to avoid one death was 125. Funnel plot inspection showed no evidence of publication bias (Online Supplementary Material Fig. S4).

The pooled data from ten trials (1820 patients) [5,6,8,15,17–22] showed a statistically significant reduction in PE recurrence for thrombolysis compared with heparin (1.1% vs 2.5%; OR 0.44, 95% CI 0.21-0.92, I^2 0%) (Fig. 4). NNT to avoid one PE recurrence was 72.

For the composite outcome of all-cause death or PE recurrence, pooled data from the eleven trials showed a statistically significant reduction for thrombolysis compared with heparin (2.4% versus 4.4%; OR 0.55, 95% CI 0.33 to 0.93, I^2 0%) (Fig. 5). NNT to avoid one death or PE recurrence was 50 patients.

Pooled data from the eleven trials showed a reduction in fatal PE for thrombolysis compared with heparin (0.8% versus 2.1%; OR 0.41, 95% CI 0.19 to 0.89, I^2 0.0%) (Fig. S5 in the Online Supplementary Material). NNT to avoid one fatal PE was 77 patients.