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Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: A systematic review and meta-analysis

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ABSTRACT

Background and Objective: According to US Food and Drugs Administration (FDA), 2 hour recombinant tissue plasminogen activator (rt-PA) 100 mg infusion is recommended for eligible patients with acute pulmonary embolism (PE). However,there exists evidence implying that a lower dosage of rt-PA can be equally effective but potentially safer compared with rt-PA 100 mg regimen. The aim of this systematic review and meta-analysis is to assess the efficacy and safety of low dose rt-PA in the treatment of acute PE.
Material and Method: We searched Pubmed, EMBASE, the Cochrane library and CBM Literature Database for randomized controlled trials (RCT) focusing on low dose rt-PA for acute PE. Outcomes were described in terms of changes of image tests and echocardiography, major bleeding events, all-cause death, and recurrence of PE.
Results: Five studies (440 patients) were included, three of which compared low dose rt-PA (0.6 mg/kg, maximum 50 mg or 50 mg infusion 2 h) with standard dose (100 mg infusion 2 h). There were more major bleeding events in standard dose rt-PA group than in low dose group (OR 0.33, 95%CI 0.12-0.91;$P = 0.94$,$I^2 = 0\%$), while there were no statistical differences in recurrent PE or all cause mortality between these two groups. Two studies compared low dose (0.6 mg/kg, maximum 50 mg/2 min bolus or 10 mg bolus, ≤40 mg/2 h) with heparin. There was no significant difference in major bleeding events (OR 0.73, 95% CI 0.14-3.98;$P = 0.72$), recurrent PE or all cause mortality. No dose-related heterogeneity was found for all the included studies.
Conclusions: The results of this meta-analysis were hypothesis-generating. Based on the limited data, our systematic review suggested that low dose rt-PA had similar efficacy but was safer than standard dose of rt-PA. In addition, compared with heparin, low dose rt-PA didn't increase the risk of major bleeding for eligible PE patients.

Introduction

Acute pulmonary embolism(PE) is a critical cardiopulmonary condition associated with high mortality and morbidity [1]. Thrombolytic therapy is considered to be the most effective treatment for high risk/life-threatening PE, and could also be effective for some intermediate risk PE with right ventricular dysfunction and/or myocardial damage [2]. Due to the high frequency of clinically relevant bleeding after intravenous thrombolysis, especially intracranial hemorrhage (ICH) and additional death, some experts still argue that the role of thrombolytic therapy in the treatment of PE remains uncertain [3].

Recombinant tissue plasminogen activator (rt-PA) is currently the most commonly used thrombolytic therapy for PE. However, it carries a significant dose-dependent risk of bleeding, thus optimal dosing could maximize benefits and minimize bleeding complications [4]. The efficacy of intravenous rt-PA at a dose of 100 mg in 2 h has been evaluated in several studies. This regimen has been approved by US Food and Drugs Administration (FDA) and also recommended by American College of Chest Physicians (ACCP) and European Society of Cardiology (ESC) guidelines for the treatment of eligible patients with acute PE [2,4]. Although this dose is effective, it has been suggested in several studies to have significantly more major hemorrhagic complications [5,6].

The effectiveness of rt-PA in patients with PE has been evaluated with doses ranging from 0.6 mg/kg to 100 mg [7–10]. It has been

Abbreviations: ACCP, American College of Chest Physicians; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomographic pulmonary angiography; ESC, European Society of Cardiology; FDA, Food and Drugs Administration; ICH, intracranial hemorrhage; LMWH, low molecular weight heparin; PE, pulmonary embolism; RCT, randomized controlled trials; rt-PA, recombinant tissue-type plasminogen activator; sPAP, systolic pulmonary artery pressure; PA, pulmonary angiography; UFH, unfractionated heparin; V/Q, ventilation perfusion.

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suggested that lower dose of thrombolysis could be used with equal efficacy and potentially less bleedings [8]. Recent studies have evaluated the low dose rt-PA (50 mg/2 h) regimen for acute PE patients with unstable hemodynamic state and/or massive pulmonary artery obstruction, showing that low dose rt-PA regimen can reduce risk of bleeding but maintain similar efficacy in these patients [8].

In this study, we conducted a systematic review and meta-analysis to assess the efficacy and safety of low dose rt-PA (50 mg/2 h or 0.6 mg/kg, max 50 mg bolus) for the treatment of acute PE, compared with heparin and standard dose (100 mg/2 h) of rt-PA. This review attempted to address some of the previous uncertainties in the treatment selections of acute PE.

Methods

Information Sources

In order to identify all randomized clinical trials on low dose rt-PA for the treatment or pulmonary embolism, we searched Pubmed (1966 through February 2013), EMBASE (1974 through February 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) in Cochrane library (last searched Issue 2 2013) and Chinese BioMedical Literature Database (CBM, 1978 through February 2013). The search terms included pulmonary embolism, thromboembolism, thrombolysis, fibrinolysis, recombinant tissue plasminogen activator, rt-PA, alteplase. If appropriate, medical heading terms were used, such as Mesh and Emtree words. For Pubmed, Embase, and CBM, the filters for randomized controlled trial were applied in the search. There were no restrictions in language and publication date. Bibliographies of included articles were checked for further studies. We also contacted main authors and pharmaceutical companies to make sure whether there were any unpublished data.

Inclusion Criteria and Study Selection

The inclusion criteria were as follows: 1) Population: patients were diagnosed objectively as acute PE. 2) Intervention: two interventional groups were assessed: low dose (0.6 mg/kg or 50 mg) of rt-PA vs. unfractionated heparin(UFH) or Low molecular weight heparin(LMWH); low dose (0.6 mg/kg or 50 mg) of rt-PA vs. standard dose (100 mg) of rt-PA. 3) Outcome: the included studies must have the following clinical outcomes: death, PE recurrence, hemorrhage and evaluation of imaging tests after treatment. Major bleeding included cases of fatal bleeding, intracranial hemorrhage (ICH), or a drop in the hemoglobin concentration by at least 20 g/L and need blood transfusion.

Two investigators independently screened the retrieved studies based on titles, abstracts and full-texts. Disagreements between the results obtained by the investigators were resolved by a third reviewer.

Data Abstraction

Two authors independently extracted the following data in a standardized process: publication date, the safety and efficacy outcomes, and quality items. In the event of discrepancy between the results obtained by the investigators concerning data extraction, a third investigator was involved in the final decision.

Quality Assessment and Risk of Bias

Quality assessment was conducted based on the recommendations of the Cochrane handbook of systematic reviews of RCTs [11]. The items included randomization sequence generation, allocation concealment, blinding of participants, personnel and outcome, incomplete major outcome data, selective outcome reporting and other source of bias.

Statistical Analysis

The primary outcomes were major hemorrhage, recurrent pulmonary embolism and all-cause death. The secondary outcomes were changes of clot burden and pulmonary pressure after treatment assessed by imaging tests (V/Q scan, pulmonary angiography) and echocardiography.

All data were calculated by Review Manager Version 5.0. For dichotomous outcomes, results were expressed as risk ratio with 95% confidence interval (CI). For continuous variables, results were expressed as mean difference (MD) with its 95%CI. I square test were used to assess between-study heterogeneity. An I [2] estimate greater than 50% ($p < 0.05$) was regarded as indicating a high level of heterogeneity and its causes were investigated as well. According to the level of heterogeneity among trials, either fixed- or random-effect models were used where appropriate.

Results

Search Results

Fig. 1 shows the selection flow of the systematic review. We retrieved 1597 citations in total. By browsing the titles and abstracts, 16 full articles were chosen for further analysis. Then 11 articles were excluded, as 3 articles [12–14] were from one multicenter study [8], 3 studies were not RCTs [15–17] and 5 studies [5,18–21] didn't focus on low dose rt-PA. Finally, 5 studies [8,22–25] in English language with 440 patients were included in the final analysis.

Characteristics of the Included Studies

Two studies [22,23] (with 179 patients) compared low dose (0.6 mg/kg, maximum 50 mg) rt-PA with heparin, three studies [8,24,25] (with 261 patients) compared low dose (0.6 mg/kg, maximum 50 mg or 50 mg/2 h) with standard dose(100 mg/2 h) of rt-PA. In all but one most recent trial [23], the reported follow-up did not exceed 30 days in these studies. Other details were listed in Table 1. (See Table 2).

Quality Assessment and Risk of Bias

All studies described the randomization methods adequately and sufficiently. Two of the included trials [23,24] reported the method of allocation concealment. And all studies mentioned the blinding, but none of them described the details of the blinding. All outcomes were pre-specified in each trial and no selective outcome reporting were detected (Appendix Table 1). All of included studies reported that confounders were reasonably balanced across study groups. No significant heterogeneity was found in each group. However, I [2] was 49% for low-dose vs. standard-dose group in all cause mortality.This "moderate heterogeneity" was mainly due to few articles involved which could make unlethal bias.

Meta-Analysis of Clinical Outcomes: Major Bleeding, Recurrent PE and Mortality

In the subgroups of low dose rt-PA and heparin, the meta-analysis showed that there was no significant difference in major bleeding events (OR 0.73, 95%CI 0.14-3.98), recurrent PE (OR 0.13, 95%CI 0.01-2.64) or all cause mortality (OR 0.63, 95%CI 0.12-3.34) (Fig. 2).

In the subgroups of different dosages of rt-PA, there were more major bleeding events in standard dose rt-PA group than in low dose rt-PA group (OR 0.33, 95%CI 0.12-0.91), while there were no statistical differences in recurrent PE (OR 0.96, 95%CI 0.30-3.04) or all cause mortality (OR 0.88, 95%CI 0.23-3.37) between these two groups (Fig. 3). The major bleeding events were listed in the Appendix Table 2.