Recombinant tissue plasminogen activator plus heparin compared with heparin alone for patients with acute submassive pulmonary embolism: one-year outcome

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Abstract

Objective To evaluate the long-term effects of thrombolysis on patients with submassive pulmonary embolism (PE). Methods Data of 136 patients with acute submassive PE and low risk of bleeding were prospectively collected from January 2005 to October 2011 in a single medical center. Patients received recombinant tissue plasminogen activator (r-tPA) plus low molecular weight heparin (LMWH, TT group, n = 79) or LMWH alone (AT group, n = 57), depending on treating physician’s recommendation and patient’s preference. Echocardiography was performed at admission, 24 h, 6 and 12 months to evaluate right ventricular function. Computed tomography pulmonary angiography (CTPA) and lung perfusion scan were performed on admission, at 7 days, 6 and 12 months to evaluate clot burden. Results Seventy-nine patients received r-tPA plus LMWH (TT group) while 57 received LMWH alone (AT group). The baseline characteristics and risk factors did not differ between the two groups. Respiratory rate, heart rate, and systolic blood pressure improved within two hours in both groups. Systolic pulmonary arterial pressure and tricuspid regurgitation improved to a greater extent in the TT group at 24 h, and at 12 months (P < 0.001), as compared to those in the AT group. At one week, and 12 months, clot burden decreased more in AT group, as compared to that in AT group (P < 0.001). There was no death due to bleeding in both groups. Recurrent PE were similar in both groups (2.5% in TT vs 1.8% in AT). The rates of minor hemorrhages were 6.3% in TT group and 1.8% in AT group (P < 0.05). Conclusion In submassive PE patient who has low risk of bleeding, thrombolysis plus anticoagulation can lead to greater improvement of right ventricular dysfunction and clot burden reduction as compared to anticoagulation therapy alone.

J Geriatr Cardiol 2013; 10: 323–329. doi: 10.3969/j.issn.1671-5411.2013.04.005

Keywords: Pulmonary embolism; Right ventricle dysfunction; Thrombolysis; Anticoagulation; Bleeding

1 Introduction

Patients with pulmonary embolism (PE) have different clinical courses and prognoses with different risk stratification. There are different therapeutic strategies. The 2008 European Society of Cardiology (ESC) guideline[1] recommended thrombolytic therapy for patients with high-risk PE. The indications and benefit/risk ratio of thrombolysis in submassive PE, however, is still controversial.[2-5] Recent studies suggest that thrombolytic therapy can rapidly decrease the overload of the right ventricle, prevent hemodynamic deterioration and decrease long-term chronic pulmonary hypertension[6] and reduce in-hospital and six-month right ventricle dysfunction and clinical adverse events.[7] We performed a prospective observational study to evaluate the effectiveness, safety, and indications of thrombolysis in Chinese patients with submassive PE.
lowing conditions: active bleeding, head trauma, or spontaneous intracranial bleeding within six months or ischemic stroke within two months, major surgery or biopsy within the preceding 10 days, major trauma within the preceding 10 days, neurologic surgery within the preceding one month, gastrointestinal bleeding within the preceding one month, uncontrolled high blood pressure (> 180 mmHg systolic blood pressure (SBP) or > 100 diastolic blood pressure (DBP)), thrombocytopenia (< 50,000/L), known structural cerebral vascular lesions, arterio-venous malformations, known coagulation disorders, aneurysm, brain tumor, pericardial effusion, serious liver or kidney dysfunction, known bleeding disorder, known inability to tolerate alteplase, known diabetic retinopathy, current therapy with an oral anticoagulant, current pregnancy or lactation, cancer (solid or active cancer), a life expectancy of less than 12 months because of underlying disease, or planned use of thrombolytic agents for extensive deep-vein thrombosis.

The baseline characteristics of all patients enrolled in the study were recorded, including routine blood samples, routine urine samples, blood gas analysis, blood type, activated partial thromboplastin time (APTT), activated blood clotting time (ACT), liver function, kidney function, echocardiogram, chest X-ray, and electrocardiogram (ECG).

Patients received either thrombolytic therapy combined with anticoagulation or anticoagulation alone, depending on treating physician’s recommendation and patient’s preference. Thrombolytic therapy was administered by intravenous infusion of 50 mg recombinant tissue plasminogen activator (r-tPA) over a period of two hours. Low molecular weight heparin (LMWH) was used at a therapeutic dose at the time of PE diagnosis and warfarin was administered after heparin to maintain an ACT of 180–220 s for 48 h. LMWH and electrocardiogram monitoring were stopped after the international normalized ratio (INR) reached to > 2–3 and the D-dimer level dropped to the normal range. Warfarin administration was continued after discharge and throughout the follow-up for both groups and monitored to maintain an INR from 2 to 3.

Patients were followed each 2 weeks for the first 3 months and then each month for the subsequent 9 months. D-dimer levels and ECG assessments were recorded at every follow-up. Echocardiogram assessments, CTPA, and lung ventilation/perfusion scans were reexamined at 6 and 12 months to assess the clot burden of the pulmonary artery after treatment. PE recurrence and the side effects of warfarin treatment (bleeding) were also recorded (Figure 1).

The study protocol was reviewed and approved by the Institute Ethics Committee of the Anzhen Hospital and Beijing Institute of Heart Lung and Blood Vessel Diseases.

Figure 1. Study flow chart. CTPA: computed tomography pulmonary angiography; ECG: electrocardiogram; LMWH: low molecular weight heparin; SPE: submassive pulmonary embolism; r-tPA: recombinant tissue plasminogen activator; UCG: echocardiogram.

Written informed consent was obtained from all patients. All patients were registered in the center.

The patients were followed as outpatients every week for the first month and every two weeks for the subsequent three months followed by every month for the next 12 months (total follow-up of 12 months). The clinical outcomes, D-dimer levels, and ECG assessments were recorded at every follow-up. Echocardiogram assessments, CTPA, and lung ventilation/perfusion scans were reexamined every 6 months to assess the clot burden of the pulmonary artery after treatment, and all patients were regularly followed for one year as outpatients to maintain an INR range from 2 to 3. Warfarin was used for 6 months for PE patients who had a definite history of immobilization ≥ 3 days or long travel without any other risk factors. These patients were followed up for another 6 months; their D-dimer levels were checked every 2 months, and CTPA and lung ventilation/perfusion scans were examined 6 months after warfarin withdrawal (Figure 1). Follow-up clinical evaluation was performed in a blinded manner by two physicians. The evaluation of the clot burden was performed by one nuclear medicine physician and one echocardiography expert. PE recurrence and the side effects of warfarin treatment (bleeding) were also recorded.
2.2 Right ventricular function assessment

Echocardiograms were used to assess the change in right ventricular expansion, systolic pulmonary artery pressure (SPAP), tricuspid regurgitation (TR), and the right ventricular/left ventricular ratio (RV/LV). Right ventricular dysfunction (RVD) was defined as fulfilling the following criteria: qualitative hypokinesis of the RV wall in the apical or subcostal view, tricuspid annular plane systolic excursion, paradoxical systolic septal motion or a newly developed tricuspid regurgitation (tricuspid regurgitation with jet velocity ≥ 2.5 cm/s in the absence of inferior vena cava collapse on inspiration), dilatation of the right ventricle observed as an RV end-diastolic diameter ≥ 2.2 cm or a right/left ventricle end-diastolic diameter ratio ≥ 1 in the apical 4-chamber view and/or ≥ 0.7 in the parasternal long axis or both in the absence of right ventricle hypertrophy and pulmonary hypertension.[9]

2.3 Assessment of clot burden and recanalization of the pulmonary artery

The degree of clot burden and the recanalization rate of the pulmonary artery were assessed by CTPA or a lung ventilation/perfusion scan and were classified using different statuses as follows: Status I, sign of defect in no more than one pulmonary subsegment on CTPA or a lung ventilation/perfusion scan; Status II, signs of defects reduced to 7 to 9 pulmonary subsegments or greater than 75% improvement on CTPA or a lung ventilation/perfusion scan; Status III, signs of defects reduced to 1 to 6 pulmonary subsegments or greater than 50% improvement on CTPA or a lung ventilation/perfusion scan; Status IV, no change on CTPA or a lung ventilation/perfusion scan; and Status V, worsening of the symptoms on CTPA or a lung ventilation/perfusion scan.[10]

The ventilation study was performed first through breathing in 99mTcO4- (> 37 MBq/mL), and the perfusion scan was performed using intravenous 99mTc-MAA 185–370 MBq. The positions were as follows: anterior, posterior, left anterior oblique, right anterior oblique, left post oblique, right anterior oblique, right lateral anterior, and left lateral anterior. CTPA was performed using a multidetector helical CT scanner (QXi, LightSpeed, GE Medical Systems, Milwaukee, Wisconsin) after receiving informed consent.

2.4 Endpoints of efficacy and safety

The primary endpoints were changes in RVD and SPAP acquired from the echocardiogram and clot burden shown by CTPA or a lung ventilation/perfusion scan. The secondary end points were all cause death, recurrent PTE or bleeding events. Recurrent PE was confirmed in the presence of at least one of the following criteria: (1) a new filling defect revealed by CTPA or a lung ventilation/perfusion scan or (2) sudden otherwise unexplained death.

Clinical deterioration was defined as the need for one or more of the following: catecholamine infusion for sustained hypotension or shock, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy.

Major hemorrhage events including lethal hemorrhages, such as intracranial hemorrhage, or required transfusion or intervention for hemodynamic deterioration. Minor hemorrhages events not classified as a major hemorrhage included including brushing, small ecchymoses or epistaxis, gingival bleeding, and microscopic hematuria, which were all classified as.

2.5 Statistical analysis

Continuous data were expressed as the means ± SD. Differences in continuous variables were assessed by ANOVA followed by Turkey post-hoc tests, and differences in categorical data were assessed using the chi-square test. In the case of low cell counts (< 5), Fisher’s exact test was used instead of the chi-square test, and P < 0.05 was considered to be statistically significant.

3 Results

3.1 Patient characteristics

During the study period, a total of 178 patients were diagnosed with acute PE (APTE). Four patients presented with acute massive APTE (one with lung cancer), and five were acute low-risk APTE patients. Three patients were considered to have recurrent PE up on admission (one with hepatic cancer). Of the remaining 166 acute submassive PE patients, 10 were acute submassive PE patients with only elevation brain natriuretic peptide (BNP) or troponin. Five submassive APTE patients received neither thrombolysis nor anticoagulation because of episode of cerebral infarction within two weeks. Fifteen patients were excluded due to incomplete data (2 of the 15 patients had breast cancer, and 1 had lung cancer). Four patients had atypical cerebral infarction. Finally, 136 acute submassive PE patients were included in the present. Seventy-nine of them agreed to receive thrombolysis (TT group, mean age 62.9 ± 11.6 years), and 57 patients chose to receive anticoagulants (AT group, mean age 61.7 ± 12.3 years). The baseline characteristics and risk factors did not significantly differ between the TT group and the AT group (P > 0.05) (Tables 1 and 2).

3.2 Clinical outcomes

Compared to the AT group, the TT group demonstrated
Table 1. The baseline characteristics in the TT and AT groups.

| Variable                        | TT group (n = 79) | AT group (n = 57) | P   |
|---------------------------------|------------------|------------------|-----|
| Age, yr                         | 62.9 ± 11.6      | 61.7 ± 12.3      | NS  |
| Male                            | 39 (49.4%)       | 28/49.1          | NS  |
| RR, breaths/min                 | 26 ± 5           | 27 ± 6           | NS  |
| HR, beats/min                   | 115 ± 9.8        | 114 ± 8.7        | NS  |
| SBP, mmHg                       | 115 ± 18         | 117 ± 17         | NS  |
| PaO2, mmHg                      | 60.9 ± 7.0       | 60.8 ± 9.0       | NS  |
| PaCO2, mmHg                     | 26.7 ± 4.1       | 28.5 ± 3.9       | NS  |
| PH                              | 7.48 ± 0.06      | 7.47 ± 0.08      | NS  |
| SaO2 (in room air)              | 88 ± 4           | 87 ± 6           | NS  |
| SPAP, mmHg                      | 153 ± 11         | 151 ± 10         | NS  |
| TR, cm/s                        | 297 ± 20         | 301 ± 19         | NS  |
| RV, mm                          | 33 ± 6           | 34 ± 7           | NS  |
| RV/LV                           | 1.33 ± 0.03      | 1.34 ± 0.04      | NS  |
| Syncope                         | 21 (26.6%)       | 17 (29.8%)       | NS  |
| S1-Q3                           | 37 (46.8%)       | 24 (42.1%)       | NS  |
| cRBBB                           | 10 (12.7%)       | 6 (10.5%)        | NS  |
| IRBBB                           | 21 (26.6%)       | 14 (24.6%)       | NS  |
| I-T-W (V1-V2-V3- V4)            | 27 (34.1%)       | 18 (31.6%)       | NS  |
| Echocardiograph:                |                 |                 |     |
| RV dysfunction, n (%)           | 79 (100%)        | 57 (100%)        | NS  |

Data are presented as means ± SD, or n (%). AT: anticoagulant; cRBBB: complete right bundle band block; IRBBB: incomplete right bundle band block; I-T-W: inverted T wave; PaO2: arterial partial pressure of oxygen; PaCO2: arterial carbon dioxide partial pressure; PH: arterial pH; SaO2: arterial oxygen saturation; SBP: systolic blood pressure; SPAP: systolic pulmonary artery pressure; SpO2: pulse oxygen saturation; TR: tricuspid regurgitation; TT: thrombolysis.  

Table 2. Risk factors in the TT and AT groups.

| Variable                        | TT group (n = 79) | AT group (n = 57) | P   |
|---------------------------------|------------------|------------------|-----|
| Smoker                          | 29 (36.7%)       | 20 (35.1%)       | NS  |
| Oral contraceptive pills        | 3 (3.8%)         | 2 (3.5%)         | NS  |
| Operation history               | 7 (8.9%)         | 5 (8.8%)         | NS  |
| Immobilization > 3 days or long travel | 6 (7.6%)      | 4 (7.0%)         | NS  |
| Hypertension                    | 59 (74.7%)       | 43 (75.4%)       | NS  |
| Coronary heart disease          | 48 (60.6%)       | 37 (64.9%)       | NS  |
| Diabetes                        | 46 (58.2%)       | 32 (56.1%)       | NS  |
| COPD                            | 8 (10.1%)        | 5 (13.5%)        | NS  |
| Respiratory failure             | 5 (6.3%)         | 3 (8.8%)         | NS  |
| Case with BMI > 30              | 21 (26.6%)       | 16 (28.1%)       | NS  |
| PTE family history              | 7 (8.9%)         | 4 (7.0%)         | NS  |

Data are presented as n (%). AT: anticoagulant group; BMI: body mass index; COPD: chronic obstructive pulmonary disease; PTE: pulmonary thromboembolism; TT: thrombolysis.  

3.3 Right ventricular function and SPAP

There were significant differences at 24 h in SPAP, TR, RV expansion, and RV/LV ratio between the TT and AT groups (P < 0.05). Within the AT group, there was no significant change in these variables at 24 h. At one year, SPAP and RV expansion were improved in both groups, as were TR and RV/LV ratio (P < 0.05). At one year, however, all of these variables improved greater in the TT group compared to those in the AT group (Table 3).

3.4 Clot burden and recanalization rate of the pulmonary artery

At one week, clot burden was decreased after thrombolysis compared to anticoagulation (P < 0.001). At one-year follow-up, the clot burden was lower in both groups compared to the clot burden at one week, although thrombolysis continued to show higher pulmonary artery recanalization rates compared to treatment with anticoagulant (P < 0.001, Table 5).
Table 4. Echocardiogram assessment in the TT and AT groups.

| Variables     | TT group (n = 79) | AT group (n = 57) | P  |
|---------------|------------------|------------------|----|
|               | Baseline         | 24 h later       | 1 year |
|               | (n = 79)         | (n = 57)         | (n = 79) |
|               | (n = 57)         | (n = 79)         | (n = 57) |
| SPAP, mmHg    | 56 ± 18          | 31 ± 11*         | 22 ± 10* |
| TR, cm/s      | 297 ± 20         | 161 ± 23*        | 150 ± 56* |
| RV, mm        | 33 ± 6           | 23 ± 2*          | 20 ± 3*  |
| RV/LV         | 1.33 ± 0.03      | 1.22 ± 0.04*     | 0.91 ± 0.02* |

Data are presented as means ± SD. *P < 0.05, †P < 0.001 compared with baseline in the same group; ‡P < 0.05, §P < 0.001, TT vs. AT group at the same time.

AT: Anticoagulant group; SPAP: systolic pulmonary blood pressure; TT: thrombolysis; TR: tricuspid regurgitation; RV/LV: right ventricular/left ventricular ratio.

Table 5. Changes in the clot burden in the pulmonary artery in the TT and AT groups.

| Variables     | TT group (n = 79) | AT group (n = 57) | P  |
|---------------|------------------|------------------|----|
|               | One week         | One year         |    |
|               | (n = 79)         | (n = 57)         | (n = 79) |
|               | (n = 57)         | (n = 79)         | (n = 57) |
| Status I      | 2 (2.5%)         | 0                | NS  |
|               | 9 (11.4%)        | 2 (3.5)*         |    |
| Status II     | 10 (17.5%)       | 61 (77.2%)       | 16 (28.1%) |
| Status III    | 35 (61.4%)       | 8 (10.1%)        | 34 (59.6%) |
| Status IV     | 12 (21.1%)       | 1 (1.3%)         | 5 (8.8%)  |
| Status V      | 0                | 0                |    |

5*P < 0.05, †P < 0.001, TT vs. AT group at the same time. AT: Anticoagulant group; TT: thrombolysis.

3.5 Bleeding events

The bleeding rate in the TT group was higher than that of the AT group, which was driven entirely by higher rates of minor hemorrhage. Five minor hemorrhage events were observed in the TT group: two small ecchymoses, one epistaxis, and two gingival bleeding episodes. There was one patient with epistaxis in the AT group (5 vs. 1, P < 0.05, Table 6). There were no major or lethal hemorrhage events in either of the two groups during hospitalization or follow-up.

Table 6. Clinical outcome events during follow-up in the TT and AT groups.

| Variables                        | TT group (n = 79) | AT group (n = 57) | P  |
|----------------------------------|------------------|------------------|----|
| Death                            | 0                | 0                | NS  |
| Recurrent PE                     | 2 (2.5%)         | 1 (1.8%)         | NS  |
| Minor hemorrhage                 | 5 (6.3%)         | 1 (1.8%)         | P < 0.05 |
| Major hemorrhage                 | 0                | 0                | NS  |
| Dysfunction of right ventricle at one year | 6 (7.6%)  | 9 (15.8%)   | P < 0.001 |

Discussion

Our study demonstrated that thrombolysis improved both short- and long-term outcomes in patients with submassive PE, without increasing major bleeding events. It provided useful data for guiding the treatment of acute submassive PE.

4.1 The initial screening conditions in our plan were suitable for the patients with submassive PE.

The current rate of the reported cerebral hemorrhaging induced by thrombolysis is approximately 3%–20%.[11,12] At present, there are still no definite conclusions on how to select the submassive PE patients for whom it would be suitable to receive thrombolysis.[6,13] The main challenge of thrombolysis is bleeding, particularly intracranial hemorrhage. In our study, no lethal bleeding events occurred. The incidence rates of minor bleeding were 6.3% and 1.8% in the TT group and the AT group, respectively. The lower rate of bleeding may be attributable to the evaluation of the intracranial condition before thrombolysis, including the presence of a recent atypical cerebral infarction or an atypical traumatic cerebral hemorrhage. In addition, for a routine contraindication, all patients who received thrombolysis before enrolling in the study must have received a skull CT scan to evaluate possible head trauma as a result of syncope after an episode of acute PTE, asymmetrical limb weakness, or dysphagia or incoordination. Our study identified four patients with acute cerebral infarction and one with a traumatic cerebral hemorrhage. In addition, for a routine contraindication, all patients who received thrombolysis before enrolling in the study must have received a skull CT scan to evaluate possible head trauma as a result of syncope after an episode of acute PTE, asymmetrical limb weakness, or dysphagia or incoordination. Our study identified four patients with acute cerebral infarction and one with a traumatic cerebral hemorrhage induced by syncope after the onset of acute PE. We can preliminarily conclude that the study design in our study is safe for submassive PE patients who will undergo thrombolysis. The inclusion criteria in our study differed slightly from a study by Jiménez, et al.[4]

4.2 Thrombolysis can improve the clinical features of submassive embolism patients

Compared with the anticoagulation group, the clinical features of the patients who underwent thrombolysis improved significantly, including the heart rate, respiratory...
rate, SBP, systolic pulmonary arterial pressure, TR, SpO2, and right ventricular enlargement at 2 h. The results demonstrated that thrombolysis could reduce the afterload of the right ventricle within 2 h. The same results were observed for SPAP, RV/LV, and TR at 24 h after thrombolysis. However, other studies have reported conflicting results regarding the earlier stages.[14,15] Our results indicated that thrombolysis is more effective than anticoagulant therapy in achieving a rapid improvement of pulmonary perfusion and regression of RVD in patients with acute PE. RVD, as assessed echocardiography, has been shown to be a predictor of adverse outcomes in patients with PE,[16] and thus, we assessed echocardiography, has been shown to be a predictor of regression of RVD in patients with acute PE. RVD, as assessing echocardiography, has been shown to be a predictor of adverse outcomes in patients with PE.[16] and thus, we can offer thrombolysis to submassive PE patients with RVD. Studies have demonstrated that 50 mg and 100 mg of r-tPA can offer thrombolysis to submassive PE patients with RVD. However, other studies have reported conflicting results regarding the earlier stages.[14,15] Our results indicated that thrombolysis could reduce the afterload of the right ventricle at 2 h. The results demonstrate that 50 mg and 100 mg of r-tPA have the same efficacy in Chinese patients,[17] and a 2-h urokinase regimen has been shown to have the same effect as recombinant tissue-type plasminogen activator.[18] However, unlike our study, the aim of these two studies was to discuss the optimal dose for high-risk PTE patients.

4.3 Clot burden is reduced by thrombolysis within one year without increasing the severe complication rate

The CTPA and lung ventilation/perfusion scan results indicated that the clot burden was decreased by thrombolysis at one week and one year. The rate of pulmonary artery recanalization reached 93.4% after one week and 98.7% after one year in the TT group and 78.9% after one week and 91.2% after one year in the AT group. These results are in agreement with other studies.[6,19] Nonetheless, thrombolysis did not reduce 30-day mortality or the recurrence of submassive PE, as previously reported.[20–22]

4.4 Conclusions

Our study suggests that thrombolysis is safe and effective for the treatment of submassive PE patients without hemodynamic compromise among Asian populations. However, an atypical cerebrovascular accident must be excluded before providing therapy. The results of our study demonstrate that thrombolysis can reduce clot burden and significantly improve the recanalization rate of the pulmonary artery after hospitalization in a year follow-up period. We believe that thrombolysis in patients who present RVD should merit consideration of thrombolysis. Our data do not indicate that thrombolysis can increase mortality or PE recurrence.

The limitations of this study are that our data were obtained from only a single center, and the study was an observational study. Large-scale randomized trials may confirm whether submassive PE patients can benefit from thrombolysis.

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