Thrombolysis With a Novel Modified Tissue-Type Plasminogen Activator, Monteplase, Combined With Catheter-Based Treatment for Major Pulmonary Embolism

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Background  A novel modified tissue-type plasminogen activator, monteplase, has been approved for acute major pulmonary embolism (PE) in Japan. Monteplase has rapid and sustained lytic effects because of a steep rise in concentration after bolus infusion and a longer half-life.

Methods and Results  To assess the efficacy and safety of thrombolysis with monteplase in combination with catheter-based treatment, acute hemodynamic changes and clinical outcomes were assessed in 50 patients with angiographically confirmed major PE. Thrombolysis with monteplase in combination with embolus fragmentation and thrombectomy was the acute phase treatment. The study population comprised 31 females and 19 males (mean age 62 years). All patients had right ventricular (RV) overload; 12 patients presented in shock. The mean pulmonary artery pressure decreased significantly from 32±9 mmHg to 25±6 mmHg after acute phase treatment (P<0.0001). The mean dosage of monteplase was 12,265 IU/kg. Death at 30 days occurred in 3 patients (6%). Major bleeding occurred in 12 patients (24%). RV overload at discharge remained in only 3% of the patients with typically acute onset.

Conclusions  Thrombolysis with monteplase, in combination with catheter-based treatment, is an effective and safe therapy for major PE. (Circ J 2009; 73: 106–110)

Key Words: Modified tissue-type plasminogen activator; Pulmonary embolism; Thrombolysis

Major pulmonary embolism (PE) is a life-threatening disorder with high mortality and morbidity.1–3 Most of the deaths of patients presenting in shock occur within the first hour after presentation,1 so rapid therapeutic action is essential to save lives. Thrombolysis with a tissue-type plasminogen activator (t-PA) produces a much faster improvement in vascular obstruction and hemodynamics than heparin treatment4 and is the established treatment for acute major PE. In Japan, a novel modified t-PA, monteplase, was approved in 2005 for high-risk patients with acute PE. Compared with the properties of native t-PA, the third-generation, bioengineered thrombolytic agent, monteplase, has a longer half-life, greater clot sensitivity, and more rapid lytic capacity. In a double-blinded, randomized study of patients with acute myocardial infarction, monteplase administration led to greater rates of coronary recanalization and at an earlier stage than was achieved with native t-PA. Initial experience of thrombolysis with the third-generation agents for acute PE has been reported,7,8 the efficacy and safety of the third-generation thrombolytic agents, including monteplase, with or without catheter-based treatment in patients with major PE has not been clarified and were examined in the present study.

Methods

Patient Population  All patients referred with symptoms suggestive of acute major PE were considered for inclusion in the study. Major PE included massive and submassive types in severity;9 definitions followed the guideline of the European Society of Cardiology.10 Massive PE involves shock or hypotension and the subgroup of patients with submassive PE can be identified by the echocardiographic findings of right ventricular (RV) overload without hypotension. All patients had confirmation of PE by pulmonary angiography. A total of 50 patients were included in the study between June 2003 and March 2008. During the same period, 13 patients with major PE were not included because of a contraindication to thrombolytic therapy (n=4), use of urokinase as the initial thrombolytic agent (n=5), anticoagulation only with unfractionated heparin (n=3), and 1 death soon after admission.

Treatment Regimen and Assessment of Efficacy  Of the 50 patients, 46 received monteplase (Cleactor, Eisai, Japan) through a catheter tip placed in the most diseased segment of the pulmonary artery and 4 were adminis-
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As soon as PE was suspected, intravenous unfractionated heparin was started with a bolus dose of 3,000–5,000 IU, followed by continuous infusion with 15,000–24,000 IU/day. Semi-emergency pulmonary angiography with catheter-based treatment was performed with femoral venous access. Catheter-based treatment included the following procedures:15 (1) catheter-directed thrombolysis with monteplase administered from the catheter tip, usually before and after embolus fragmentation; (2) embolus fragmentation using a 6Fr K-PA pigtail catheter (Medikit; Tokyo, Japan), which has a side-hole in the curvature of the pig-tail loop that allows passage of a guide wire; the pigtail is rotated manually over the fixed wire and simultaneously moved back and forth; (3) thrombectomy by aspirating the thrombus using a 8Fr percutaneous transluminal coronary angioplasty guiding catheter (Judkins right guide size 4) through a long sheath inserted into the main pulmonary artery; (4) temporary inferior vena cava filter placement until the severity of deep vein thrombosis (DVT) was determined. Continuous urokinase infusion was systemically started with 480,000 IU/day. The duration of infusion was determined by the amount of residual thrombus and the severity of DVT, evaluated by venography. A permanent inferior vena cava filter was implanted whenever possible. After stabilization of the patient’s general condition, oral warfarin therapy for more than 6 months was begun at an international normalized ratio of prothrombin time of 2.0–3.0.

Statistical Analysis

Analyses were performed with StatView software version 5.0 (SAS Institute Inc, Cary, NC, USA). Continuous variables are expressed as the mean±SD or median. Dichotomous variables are expressed as percentages. Statistical comparisons of continuous variables were performed by the Student’s t-test or Mann-Whitney’s U test, as appropriate. Statistical comparisons of dichotomous variables were performed by the chi-square test or Fisher’s exact test, as appropriate. All probability values were 2-tailed, and values less than 0.05 were considered statistically significant.

Results

Patients’ Baseline Characteristics

The study group comprised 50 patients with major PE of which 37 were allocated to Group A and 13 were Group B (31 females, 19 males; mean age 62 years). The duration of symptoms was shorter in Group A than in Group B (0 vs 9 days (median), P<0.01). Cancer (32%) was the most

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (n=37)</th>
<th>Group B (n=13)</th>
<th>Total (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±14</td>
<td>61±17</td>
<td>62±15</td>
</tr>
<tr>
<td>Duration of symptoms (median, days)</td>
<td>0 (0–14)*</td>
<td>9 (0–45)</td>
<td>2 (0–45)</td>
</tr>
<tr>
<td>Cancer</td>
<td>14 (38%)</td>
<td>2 (15%)</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Postoperation</td>
<td>7 (19%)</td>
<td>2 (15%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>2 (5%)</td>
<td>1 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Shock</td>
<td>10 (27%)</td>
<td>2 (15%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4 (11%)</td>
<td>1 (8%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Requiring PCPS</td>
<td>5 (14%)</td>
<td>1 (8%)</td>
<td>6 (12%)</td>
</tr>
</tbody>
</table>

Data are no. (%) or mean±SD, unless otherwise indicated. *P<0.01 (comparison with Group B). PCPS, percutaneous cardiopulmonary support.

The effectiveness of thrombolysis with monteplase was assessed as improvement of hemodynamics and gas exchange indices in the acute phase, as well as the clinical outcome. Vital signs and arterial blood gas analysis were measured at admission and after thrombolysis with catheter-based treatment. Pulmonary artery pressure was obtained directly with a pigtail catheter in the pulmonary artery just before and immediately after thrombolysis with catheter-based treatment. Because the efficacy of thrombolysis differs according to whether or not the patient has cardiopulmonary disease, we differentiated patients free of significant cardiac, pulmonary and chronic thromboembolic disease (Group A) from those presenting with these conditions (Group B). Patients were considered as having chronic thromboembolism preceding an acute episode if they met at least 1 of the following criteria: (1) symptoms suggestive of PE >1 month before admission, (2) mean pulmonary artery pressure >40 mmHg at admission, and (3) angiographic features of chronic thromboembolism.11,12 Standard color 2-dimensional echocardiographic Doppler examinations were performed to assess RV function on admission and before discharge. RV overload was defined as RV dilatation (ie, the right ventricle appeared larger than the left ventricle in the apical view or maximum velocity of tricuspid regurgitation >2.8 m/s) on echocardiography.10 Major bleeding was defined as bleeding that required blood transfusion or surgical control, or hemorrhagic stroke.11 The alveolar–arterial oxygen pressure difference (AaDO2) was calculated as:

\[
\text{AaDO}_2 (\text{mmHg}) = \text{PAO}_2 – \text{PaO}_2
\]

\[
\text{PAO}_2 = (\text{P}_\text{H}_2\text{O}) \times (\text{FiO}_2) – 1.25\text{PaCO}_2
\]

and the alveolar–arterial oxygen tension ratio (a/APO2) as:

\[
\text{a/APO}_2 = \frac{\text{PaO}_2}{\text{PAO}_2}
\]

where \(\text{P}_\text{H}_2\text{O}\) is barometric pressure (assuming 760 torr), \(\text{P}_\text{r}\text{cO}_2\) is the water vapor partial pressure (47 torr at 37°C), \(\text{FiO}_2\) is fractional inspired oxygen concentration, \(\text{PaCO}_2\) is partial pressure of carbon dioxide in arterial blood (mmHg), \(\text{PaO}_2\) is partial pressure of oxygen in arterial blood (mmHg), and \(\text{PAO}_2\) is partial pressure of oxygen in the alveoli.13 Information regarding demographic and clinical characteristics, medical history, management strategies, therapeutic effects, and outcomes was collected from the medical records.
common preexisting disorder. All patients had RV overload, and 12 patients (24%) presented in shock; 10 patients (20%) had comorbid conditions with a relative contraindication for thrombolytic therapy, including recent surgery (n=7), octogenarian (n=2) and pregnancy. There were no significant differences between the 2 groups in age, gender, concomitant disease or severity (Table 1).

Mean pulmonary artery pressure in Group B was significantly higher than in Group A (43±6.0 mmHg vs 29±4.6 mmHg, P<0.0001). Systolic blood pressure was significantly reduced in both groups by thrombolysis with catheter-based treatment in all patients. Post mean pulmonary artery pressure were significantly reduced in both groups by thrombolysis with catheter-based treatment (P<0.0001). Post mean pulmonary artery pressure was higher in Group B than in Group A (31±5.8 mmHg vs 22±4.6 mmHg, P<0.0001). Systolic blood pressure was significantly elevated in Group A by thrombolysis with catheter-based treatment (P=0.007). In the arterial blood gas analysis, PaO₂, PaO₂/FiO₂, and a/APO₂ were significantly improved by thrombolysis with catheter-based treatment (Table 2). Additional systemic infusion of urokinase was used in 44 patients (88%), DVT, detected in a mean of 3 days after admission, was found in 42 patients (84%). A temporary inferior vena cava filter was implanted in 47 patients (94%) and was removed after a median of 3 days (range 1–12). A permanent inferior vena cava filter was placed in 11 patients (22%), RV overload at discharge was observed more frequently in Group B than in Group A (62% vs 31%, P<0.0001) (Table 3).

Adverse Events
Major bleeding occurred in 12 patients (24%) (Table 3); 1 patient had fatal re-bleeding from the site of a subdural hematoma on the day following monteplase use: although that patient had developed a massive PE on day 2 postsurgery, thrombolitics were administered because catheter-based treatment was not successful. The other causes were bleeding from the cannulated site of percutaneous cardio-pulmonary support (n=5), unknown (n=2), hemothorax, peritoneal hematoma, bleeding from surgical site, and hemoptysis. Hemoptysis was suspected to be related to perforation of pulmonary artery caused by manipulation of a guidewire and was staunched by percutaneous embolization with gelfoam.

Short- and Long-Term Outcomes
Three patients from Group A died at 30 days (Table 3), 1 as a result of persistent cardiogenic shock, another with parathyroid cancer who died suddenly at day 22 and was
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Diagnosed at autopsy as having recurrent PE with a massive thrombus from the iliac vein to the pulmonary artery beyond the inferior vena cava filter, and the 3rd patient died after intracranial re-bleeding from a subdural hematoma at the surgical site of. Nonfatal recurrence during hospitalization was diagnosed in 1 patient on the basis of clinical symptoms related to intracardiac thrombus.

Follow-up information after 30 days was obtained for 44 patients (mean follow-up 19.5 months, range 1–59). Five patients from Group A died during follow-up: the causes of death were cancer (n=3), myocardial infarction (1), and spinocerebellar degeneration (1). Recurrent PE was not observed during the follow-up period. Long-term follow-up information available for 24 from Group A and 12 from Group B; the 24 patients from Group A and 7 patients from Group B showed no signs of cardiac or pulmonary functional limitation; the 5 other patients from Group B complained of exertional dyspnea (New York Heart Association class II, 4 patients; class III, 1 patient).

Discussion

To the best of our knowledge, the present study is the first to report on the efficacy and safety of the third-generation thrombolytic agents in patients with major PE. Thrombolysis with monteplase, in combination with catheter-based treatment, showed rapid reduction of heart rate and pulmonary artery pressure, improvement of the gas exchange indices, and favorable outcomes.

Major PE is a life-threatening disorder with a high mortality and morbidity. The 30-day mortality observed in this study (6.0%) is lower than that reported by the ICOPER investigators (11.4% at 2 weeks) and by a recent single-center cohort receiving thrombolytic therapy for major PE (8.8%) In-hospital prognosis was related to the initial severity of PE, as defined by the clinical presentation, in particular hemodynamic instability, including RV dysfunction. In the recent registry of the Japanese Society of Pulmonary Embolism Research, 30-day mortality among patients presenting in shock was 15.6% and among patients with cardiac arrest, 52.4%. Since 25% of the present study population was in an unstable condition with shock, the 30-day mortality would be thought a satisfactory result.

RV overload has been shown in previous studies to regress after thrombolytic therapy, and rapid recovery of RV function is associated with reduced morbidity and mortality. In the present study, a 23% reduction in the mean pulmonary artery pressure, indicating RV afterload, was obtained by thrombolysis with catheter-based treatment. Another study of a hybrid treatment, the same as the present catheter-based treatment with a second-generation thrombolytic agent (tisokinase), showed approximately equal effects in reducing pulmonary artery pressure. Monteplase has a longer half-life, enabling high effective plasma concentrations after bolus injection in the early phase. In a canine model of life-threatening acute PE, the reduction in mean pulmonary artery pressure 30 min after treatment was greater in the monteplase group (~20%) than in the alteplase group (~6%). The third-generation thrombolytics have a more rapid effect than the second-generation agents, which is better for saving the life of the critical patient with major PE.

Significant improvement of the gas exchange indices, including PaO2, PaO2/FiO2, and a/APO2, was observed after thrombolysis with catheter-based treatment, which would have resulted from the rapid resolution of pulmonary emboli by thrombolysis. The a/APO2, which is relatively unaffected by FiO2 than aAO2, was adapted as an index of gas exchange because patients with major PE present with severe hypoxia and require high-concentration oxygen treatment.

The mean dose of monteplase used in the present study was approximately half of the generally recommended dose. Catheter-directed thrombolysis permits a high concentration of drug to be delivered directly into the thrombus, resulting in shorter infusion times and lower doses of the drug. Furthermore, the combination of catheter embolus fragmentation and thrombectomy has a synergistic effect because it increases both the thrombus surface area exposed to lytic drugs and the ease of aspirating the thrombus. In the present study, RV overload persisted in only 1 patient (3.1%) among those without concomitant cardiopulmonary disease and this favorable result may be related to the early effect of monteplase with catheter-based treatment.

The rate of major bleeding in this study (24%) is comparable with that reported in 132 thrombolysed patients from a tertiary care hospital in Paris (25%) but slightly higher than that reported in the thrombolytic arm of the MAPPE registry (21.9%) and in 304 patients from the International Cooperative Pulmonary Embolism Registry who received thrombolysis (21.7%). The risk of bleeding in patients with submassive PE would seem to be equal or greater than the benefits of thrombolysis. The rate of bleeding in the present study requires careful consideration, because approximately 75% of the present study population had submassive PE in severity. In the treatment of myocardial infarction, the rate of bleeding complications with the use of intravenous third-generation thrombolytic drugs is even lower than those with recombinant tissue plasminogen activator and other agents presumably as a result of its higher affinity and specificity for bound fibrin. Potentially, the substitution of monteplase in combination catheter-based treatment could result in faster lysis and further reduction of bleeding complications. The higher rate of bleeding than expected in the present study could be the result of having more patients with comorbid risks for bleeding and those with a relative contraindication to thrombolysis. Catheter-based treatment is best for patients at risk of bleeding although it is reported that invasive procedures are an independent factor for major bleeding.

Study Limitations

The results require careful interpretation. Firstly, the study was retrospective, had a relatively small number of patients, and did not have a comparative group of patients who were not undergoing thrombolysis with monteplase. However, the incidence of massive PE is very low, even in large centers. Secondly, definitive evidence of the efficacy of catheter-based treatment is not fully established. Furthermore, catheter-based treatment necessitates skilled
interventionists as integral members of the interdisciplinary team required for successful management of major PE. Thirdly, because the indication for thrombolysis in patients with submassive PE is debatable, the treatment of these patients in the present study is possibly an over-indication.

In conclusion, in our experience, thrombolysis with monteplase in combination with catheter-based treatment is effective and safe in patients with major PE. The adaptation of this treatment requires further study in a large group of patients and in additional centers with expertise in the management of such patients.

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References