Efficacy of Alteplase Thrombolysis for ED Treatment of Pulmonary Embolism With Shock

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Our objective was to assess efficacy and tolerance of thrombolysis using 0.6 mg/kg of Alteplase in patients with massive pulmonary embolism defined as the association of a pulmonary embolism with shock. We retrospectively included 21 patients presenting with a massive pulmonary embolism confirmed by either scintigraphy or spiral computed tomography. Patients were treated on the basis of a standard rationale followed by thrombolysis with 0.6 mg/kg Alteplase over a period of 15 minutes. Hospital mortality, vital signs before and 2 hours after thrombolysis, and incidence of hemorrhagic events were recorded. Five patients (23.8%) died, 4 of these deaths occurred during the first 4 hours after hospital admission. Systolic and diastolic blood pressure (Sp02) were significantly improved 2 hours after the beginning of thrombolysis. Five minor hemorrhagic events occurred. This study demonstrates that for patients with pulmonary embolism and shock, a bolus treatment with Alteplase is potentially effective and well tolerated. (Am J Emerg Med 2003;21:438-440. © 2003 Elsevier Inc. All rights reserved.)

Massive pulmonary embolism (MPE) is rarely encountered in EDs. Immediate management is essential, otherwise the condition could be fatal at an early stage. In the case of MPE, clinical suspicion is often very high, with sudden onset of acute dyspnea, chest pain, or syncope. Physical examination is often poor or nonspecific and chest x-rays are often noncontributive. A confirmatory procedure following the guidelines of the European Society of Cardiology is therefore necessary. Management of MPE is based on symptomatic treatment and thrombolysis in the absence of contraindications. Although the efficacy of thrombolysis versus heparin in MPE has not been formally proven in large prospective, randomized studies, thrombolysis is probably effective in terms of reducing early mortality.1-3

The objective of this work was to retrospectively assess the efficacy and tolerance of thrombolysis by Alteplase (Boehringer Ingelheim, Germany) administered on the basis of the simplified algorithm described by Sors and Goldhaber4,5 in a series of 21 patients with MPE managed in our ED. This simplified algorithm consisted of the administration of 0.6 mg/kg Alteplase over 15 minutes, although the standard regimen is an intravenous bolus of 10 mg followed by an infusion of 90 mg over 2 hours.

PATIENTS AND METHODS

Patients

Twenty-one patients presenting with massive pulmonary embolism between 1996 and 2000 were included in this retrospective study. Patients were selected using the hospital’s pharmacy database. Massive pulmonary embolism was defined as a pulmonary embolism suspected on the basis of clinical probability confirmed by one of the following procedures: ventilation perfusion scintigraphy, spiral thoracic computed tomography (CT) scan, transthoracic ultrasound, and combined with a state of shock. Shock was defined as a systolic blood pressure below 90 mm Hg or a drop of 40 mm Hg in relation to the patient’s normal blood pressure not resulting from sepsis or a concomitant rhythm disorder.6

Diagnostic and Therapeutic Approach

A strong clinical probability of embolism was found in all patients. An emergency imaging procedure, confirming the clinical diagnosis, was then performed. Patients were managed on the basis of a standardized rationale previously written.

Symptomatic treatment included fast-flow oxygen therapy, initial intravenous fluid loading with 500 mL of macromolecular solution in the absence of signs of major right heart failure followed by dobutamine at incremental doses. All the patients were also submitted to noninvasive monitoring for blood pressure, heart rate, breathing, and O2 saturation.

Thrombolysis was prescribed if there was no absolute or relative contraindications. A dose 0.6 mg/kg Alteplase was administered over a period of 15 minutes, with a maximum dose not exceeding 50 mg. After this, an intravenous heparin infusion was started at a dose of 400 IU/kg per day as soon as the patient’s partial thromboplastin time, taken every 2 hours, dropped below twice the control value.

DATA COLLECTION AND STATISTICAL ANALYSIS

Data were obtained from ED records, computerized on Access (Microsoft, Seattle, WA) then processed on Epi Info
SpO2 (%) 86

Discussion

Diagnosis of pulmonary embolism is a daily challenge for ED physicians. Articles recently published, proposing different diagnostic algorithms, show that this issue has not yet been completely resolved.6-10 The situation is different in cases of strongly suspected massive pulmonary embolism with shock. The most useful initial test is cardiac ultrasound as recommended by the European Society of Cardiology.6 However, lack of local availability leads us to use ventilation perfusion scintigraphy or spiral thoracic CT scan. These procedures were available in less than 1 hour for all patients. Scintigraphies all made a contribution to the diagnosis, contrary to the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study,11 but our series only included massive pulmonary embolisms with perfusion amputations close to 50% which could account for the better results.

Treatment of the symptoms initially included intravenous fluid loading for patients without signs of major right heart failure and dobutamine, as recommended in the literature.5,12,13

Although recommended by various scientific societies6 and accepted by the Food and Drug Administration, thrombolysis has not yet proven its efficacy on mortality over heparin in cases of massive pulmonary embolism in large therapeutic trials.3 The UPET (Urokinase Pulmonary Embolism Trial) study showed no superiority in terms of mortality of urokinase over heparin alone, but the cases included were not all of MPE and the large doses of thrombolytic used caused a high rate of hemorrhagic complications.14 Further therapeutic trials compared Alteplase and heparin, but included patients who were not in a state of shock. Their efficacy criteria were hemodynamic: decrease in pulmonary arterial pressure15 and improvement of right ventricular dysfunction.16 These trials demonstrated the efficacy of Alteplase on the main criteria selected but were not designed to prove a decrease in mortality. A recent trial compared Alteplase plus heparin versus heparin alone in patients with a pulmonary embolism without hemodynamic instability but with right ventricular dysfunction.17 In these patients with a “submassive” pulmonary embolism, Alteplase improved the clinical course. Only one randomized, prospective study compared streptokinase and heparin alone in patients with shock, but only included 8 patients. The 4 patients in the streptokinase arm survived, whereas those in the heparin group died.2

The rationale for the use of Alteplase at a dose of 0.6 mg/kg over 15 minutes in our department of EM came from 2 prospective, randomized studies,3,4,18 demonstrating its equivalence with the standard regimen in terms of tolerance and efficacy. However, populations of these 2 studies were hemodynamically stable. Our study is thus the first published using this modality of administration in patients with hemodynamic instability. This treatment is simpler to implement in an ED and allows the use of smaller doses of Alteplase.

In terms of efficacy, the overall inhospital mortality rate was relatively low in our patients with hemodynamic instability when compared with that of the ICOPER (International Cooperative Pulmonary Embolism Registry) group.19

In this study, 96 patients were hemodynamically unstable.

TABLE 1. Vital Signs Before and 2 Hours After Thrombolysis

<table>
<thead>
<tr>
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<th>Before Thrombolysis</th>
<th>2 Hours After Thrombolysis</th>
<th>P</th>
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<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>89 ± 13</td>
<td>121 ± 15</td>
<td>2.10^-6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>53 ± 9</td>
<td>70 ± 12</td>
<td>8.10^-5</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>98 ± 21</td>
<td>88 ± 19</td>
<td>0.10</td>
</tr>
<tr>
<td>BR (/min)</td>
<td>29 ± 7</td>
<td>25 ± 7</td>
<td>0.07</td>
</tr>
<tr>
<td>SpO2 (%)</td>
<td>86 ± 10</td>
<td>97 ± 2</td>
<td>3.10^-4</td>
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Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BR, breath rate; SpO2, O2 saturation.
and the overall mortality in this subgroup was 58.3%. Our patients clearly belonged to this category as demonstrated by their clinical status on admission. The comparison with the ICOPER study is limited, however, by the fact that no details were given in the ICOPER study about the characteristics of the subgroup of patients with hemodynamic instability and that mortality was measured 3 months after the acute episode.

Tolerance was satisfactory, with a low hemorrhagic complication rate, probably because of an absence of pulmonary angiogram or other invasive procedures. No intracerebral hemorrhage was recorded, the incidence of which was shown to be only 1.9% in a retrospective study including 312 patients. It seems essential to administer the thrombolytic agent as early as possible after diagnostic confirmation in an environment permitting constant monitoring and intensive-care procedures if required because of the high mortality rate in these patients, as demonstrated by Courtney and Kline. Patients who died from a MPE presented in the hours before an association of shock, dyspnea, alteration of mental status, and one risk factor for venous thromboembolism. A department rationale would make early identification of this small subcategory of patients easier.

This study has major limitations because of its retrospective methodology, especially with regard to bias in selection of patients and missing data in medical files. Although all patients treated by Alteplase for a MPE during the study period were included thanks to the pharmacy database, it is possible that some patients with MPE and no contraindications did not receive this treatment but only received heparin and symptomatic treatment. Diagnosis and therapeutic procedure were based on a previously written ED rationale therefore limiting the variability of treatment. In addition, the series of patients is small and does not allow us to draw any conclusion concerning the percentage of serious adverse effects and in particular cerebral hemorrhages.

CONCLUSION

This cohort study shows that treating patients presenting with pulmonary embolism and state of shock by thrombolysis using a bolus of Alteplase is potentially effective, well tolerated, and easy to implement. However, further prospective studies are required to confirm the validity of this treatment.

REFERENCES