Intrapulmonary Artery Infusion of Urokinase for Treatment of Massive Pulmonary Embolism: A Review of 26 Patients with and without Contraindications to Systemic Thrombolytic Therapy

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Summary

Background: Pulmonary emboli (PE) are a common event seen in over 600,000 patients a year. Occurring suddenly, PE often result in a high rate of mortality. To combat the high rate of mortality, more aggressive therapies including the use of thrombolytics are often indicated. The use of intrapulmonary artery infusion of urokinase has been shown to promote rapid resolution of emboli and restoration of normal pulmonary hemodynamics.

Hypothesis: The study was undertaken to review the effectiveness and safety of pulmonary artery infusion of urokinase in 26 patients with and without contraindications to the use of systemic thrombolytic therapy.

Methods: We reviewed the outcomes of 26 patients who received infusion of urokinase, using a usual loading dose of 4,000 U/kg body weight given as a bolus, followed by 4,000 U/kg/h for 12 to 24 h, using either/or unilateral or bilateral infusions. Pulmonary angiograms were obtained prior to and following the urokinase infusions.

Results: Intrapulmonary artery infusion of urokinase was given to 26 patients, 9 of whom had contraindications to the use of systemic thrombolytic therapy. Six patients were recent post operative, one was receiving oral anticoagulants, one was receiving chemotherapy with bleeding complications, and one had received cardiopulmonary resuscitation. Twenty of the patients returned to their baseline state (normal heart rate, blood pressure, and pO₂), one was minimally improved, and

five deaths occurred. Of the five deaths, three occurred within 1 h of starting urokinase infusion, the remaining two died more than 36 h after treatment with urokinase as a result of their basic underlying disease. Minor bleeding occurred from puncture sites, two hematomas occurred at the puncture site, and there were two gastrointestinal bleeds, one of which occurred a week post urokinase therapy while the patient was receiving heparin and coumadin. No central nervous system bleeds occurred and no transfusions were required as a result of urokinase intrapulmonary artery infusions. The overall mortality rate in this series was 11.5%.

Conclusions: Intrapulmonary artery infusion of urokinase in extensive pulmonary embolism is a safe and efficient treatment in patients with and without contraindication to the use of systemic thrombolytic therapy. With a usual loading dose of 4,000 U/kg body weight, followed by an infusion of 4,000 U/kg/h for 12 to 24 h, it produces significant and rapid resolution of pulmonary emboli with a low morbidity and mortality rate. In our series, the mortality rate was 11.5%, and none of the deaths was the direct result of urokinase therapy.

Key words: pulmonary emboli, thrombolytic therapy, intrapulmonary thrombolytic

Introduction

Pulmonary emboli (PE) are a common event seen by physicians in nearly every field of medicine. It is estimated that each year 600,000 patients develop PE and that 60,000 die of this complication.¹ The extent of embolism can range from unnoticeable to an acute unstable hemodynamic change within minutes. With a wide range of symptoms at presentation comes a wide range of treatment options. Failure to diagnose and treat pulmonary emboli properly can result in a high rate of mortality.

Massive PE has an overall mortality rate of 6 to 10% in total hospital deaths^{2–6} and a 37.8% mortality rate in hospital patients diagnosed with PE.⁷ Pulmonary embolism is the second most common cause of death in maternal mortality,

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reported in 35.3% of maternal deaths.⁸ Death from a massive PE is often sudden, with one study showing that 63.5% of patients with a fatal PE died within 6 h after first onset of symptoms.³ Gallerani *et al.*⁵ reported autopsy studies of 507 subjects dying suddenly outside the hospital and reported that 9.4% died from PE.

As a result of the rapid mortality associated with acute PE, more aggressive approaches, that is, thrombolytic therapy, have been attempted. Therapy with thrombolytics has shown a rapid resolution of pulmonary arterial occlusion and reduction of pulmonary artery pressure.⁹⁻¹² However, it is estimated that < 10% of patients with PE are receiving thrombolytic therapy in the United States.¹³ There is also a subset of patients with extensive PE who have contraindications to systemic thrombolytic therapy, such as recent surgery, history of cerebrovascular accident, or cardiopulmonary resuscitation. These patients face a high mortality risk. We have reviewed 26 cases in which intrapulmonary arterial infusion of urokinase for the treatment of pulmonary emboli was used in patients who are at high risk of death, including 9 patients with contraindications to systemic thrombolytic agents.

Methods

We reviewed all cases of pulmonary emboli treated with intrapulmonary arterial infusions of urokinase at University Health Systems, Pitt County Memorial Hospital, Greenville, N.C., the major teaching hospital for the East Carolina University School of Medicine, from 1984 to August 1998. Twenty-six patients (13 men and 13 women, age range 26–82 years) were treated with intrapulmonary artery urokinase and comprise the basis for this report. The general inclusion criteria were unstable patients with > 50% total lung vasculature occluded by emboli. Thirteen patients had documented main pulmonary artery pressures (MPAP) with a range of systolic 44–90 mmHg and diastolic 8–40 mmHg. The average MPAP

was systolic 58.2 mmHg and diastolic 21.5 mmHg. Only 8 of the 26 patients had documented deep vein thrombosis.

The usual loading dose of urokinase was 4,000 U/kg of body weight, followed by infusion of 4,000 U/kg body weight/h. The infusions were administered for 12 to 24 h, using either unilateral or bilateral infusions with split dosing based on the embolic location. All cases were confirmed by pulmonary angiograms prior to infusions and after completion of urokinase infusion (Figs. 1 and 2). Oral coumadin therapy and/or placement of inferior vena cava filters followed post-thrombolytic therapy.

The extent of embolization revealed by pretreatment pulmonary angiograms is shown in Table I.

No pulmonary angiogram report was present for one patient who died on the table in the radiology department.

Results

There were 26 patients with life-threatening PE who received intrapulmonary arterial infusions of urokinase. Nine of the 26 patients had contraindications to the use of systemic thrombolytic agents. Six of the patients were recent post operative. (Two patients were 6 and 8 days post coronary artery bypass grafting; one patient was 20 days post intracerebral hemorrhage with repair of aneurysm; another patient was 1 day post exploratory laparotomy; one patient was 42 days post removal of acoustic neuroma; one patient was 19 days post craniotomy.) One patient was on oral anticoagulants, one patient had received cardiopulmonary resuscitation, and one was receiving chemotherapy with radiation for oral cancer and had recurring bleeds associated with treatment. Only 8 of the 26 patients had documented deep vein thrombosis.

Following urokinase infusion, 20 patients returned to their baseline state; 1 patient was only minimally improved, and 5 deaths occurred. Within 1 h of the onset of thrombolytic therapy, three of the five deaths occurred on the radiology table as

FIG. 1 (A) Extensive embolization of the left main pulmonary artery. (B) Marked resolution and reperfusion of the left pulmonary artery post urokinase infusion.

FIG. 2 (A) Extensive embolization of the right main pulmonary artery. (B) Marked resolution and reperfusion of the right main pulmonary artery post urokinase infusion.

TABLE 1 Extent of embolization as shown by pretreatment pulmonary angiograms

Occlusion site by embolism	No. of patients
Main pulmonary artery	3
Saddle embolus	4
Left main pulmonary artery & < 50% of the right lung embolized	2
Right main pulmonary artery & < 50% of the left lung embolized	7
Bilateral with > 50% of each lung embolized	9

a result of massive emboli and cardiopulmonary collapse. The other two deaths occurred more than 36 h later, one 13 days later while the patient was in the intensive care unit and the other 36 h later secondary to heart failure.

Only one of the five patients who died had a contraindication to systemic therapy. He had a recurrent bleed secondary to oral cancer and was receiving chemotherapy and radiation; he died within 1 h of starting the intrapulmonary urokinase therapy. The patient's death was associated with acute cardiovascular collapse and not attributed to his bleed.

The one patient with only minimal improvement did not receive a bolus dose and only received an infusion at 4,000 U/kg/h. Bleeding complications included minor bleeding from puncture sites, two hematomas at puncture sites, two gastrointestinal bleeds (one occurred 7 days post urokinase therapy while the patient was on heparin and coumadin), and one episode of vaginal bleeding in a patient with uterine cancer. No central nervous system bleeds occurred and no transfusions were needed as a result of urokinase therapy.

Discussion

Massive PE constitute a life-threatening condition with a high mortality rate. Complete resolution of major PE treated with heparin alone can often take more than 3 weeks.¹⁴ Because of the sudden and often high mortality of PE, a more aggressive approach is indicated in patients who are hemodynamically unstable. Many studies have shown that thrombolytic agents effectively resolve pulmonary artery thrombi within a few hours.¹⁴ Urokinase may be the most beneficial thrombolytic agent. One study reviewed streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA) in an *in vitro* model of venous thrombolysis and found that streptokinase was the agent associated with the slowest rate of clot lysis. Urokinase was associated with an intermediate rate of clot lysis, but appeared to be the agent with the greatest degree of fibrinolytic specificity. Although rt-PA was associated with improved efficacy early in the perfusions, the differences between rt-PA and urokinase dissipated after 30 min.¹⁵

A more detailed approach to thrombolytics is the use of intrapulmonary versus systemic therapy. Four basic principles explain why intrapulmonary therapy may be better than systemic thrombolytic therapy: (1) The drug can be concentrated more in the area most needed; (2) since the thrombolytic agent is more contained there may be fewer occurrences of side effects and it could be used in patients with contraindications to systemic therapy; (3) the concentrated dose may provide a faster resolution of the clot; (4) ease of use: if an angiogram is used for diagnosis, then access is already obtained and treatment can be started immediately. The use of intrapulmonary artery urokinase and other such thrombolytics has demonstrated a rapid clearing of the embolized pulmonary vessels, decrease in pulmonary artery pressure, and improve-

ment in gas exchange in 12 to 24 h after infusion of urokinase into the pulmonary artery.^{9, 10, 16, 17}

For our report, the contraindications to systemic therapy, as defined by the maker of urokinase, are as follows: active internal bleeding, history of cerebrovascular accident, recent trauma including cardiopulmonary resuscitation, recent (within 10 days) major surgery (including obstetrical delivery and organ biopsy), intracranial neoplasm, arteriovenous malformation or aneurysm, known bleeding diathesis, and severe uncontrolled arterial hypertension. The maker of urokinase also states that the concurrent use of anticoagulants with intravenous administration of urokinase is not recommended. We, therefore, included the use of warfarin (coumadin) as a contraindication in our study.

A Medline® review of the literature does not show any studies that have used intrapulmonary thrombolytics in patients with contraindications to systemic therapy. This approach may help to save many patients, especially those who are post surgical. Our review demonstrates that intrapulmonary urokinase is safe and effective in patients with contraindications to systemic therapy; however, more studies in this area are needed.

We have demonstrated the safety and rapid benefits of using intrapulmonary arterial infusion of urokinase in patients with and without contraindications to the use of systemic thrombolytic agents. Our mortality rate, 3 of 26 patients or 11.5% of patients dying from PE, is lower than the reported mortality rate in the literature, which showed that it was 25% in patients presenting with cardiogenic shock and up to 65% in patients requiring cardiopulmonary resuscitation.^{7, 18} We only studied the seriously ill patients with life-threatening extensive embolic disease of the pulmonary system, as demonstrated by the pulmonary angiograms reported above. The two other deaths were predictable based on the severity of the patients' underlying diseases and were not directly due to their PE.

Conclusions

Intrapulmonary artery infusion of urokinase is a safe, effective, and efficient treatment for extensive pulmonary emboli in patients with and without contraindications to the use of systemic thrombolytic drugs. Intrapulmonary artery infusion of urokinase with a usual loading dose of 4,000 U/kg body weight, followed by an infusion of 4,000 U/kg body weight/h for 12 to 24 h produces significant and rapid resolution of the pulmonary artery thrombi with a low morbidity and mortality rate. In our series, the mortality rate was 11.5%, and none of the deaths were the direct result of urokinase therapy.

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