Thrombolytic Therapy in Unstable Patients with Acute Pulmonary Embolism: Saves Lives but Underused

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ABSTRACT

BACKGROUND: Data are sparse and inconsistent regarding whether thrombolytic therapy reduces case fatality rate in unstable patients with acute pulmonary embolism. We tested the hypothesis that thrombolytic therapy reduces case fatality rate in such patients.

METHODS: In-hospital all-cause case fatality rate according to treatment was determined in unstable patients with pulmonary embolism who were discharged from short-stay hospitals throughout the United States from 1999 to 2008 by using data from the Nationwide Inpatient Sample. Unstable patients were in shock or ventilator dependent.

RESULTS: Among unstable patients with pulmonary embolism, 21,390 of 72,230 (30%) received thrombolytic therapy. In-hospital all-cause case fatality rate in unstable patients with thrombolytic therapy was 3105 of 21,390 (15%) versus 23,820 of 50,840 (47%) without thrombolytic therapy ($P < .0001$). All-cause case fatality rate in unstable patients with thrombolytic therapy plus a vena cava filter was 505 of 6630 (7.6%) versus 4260 of 12,850 (33%) with a filter alone ($P < .0001$). Case fatality rate attributable to pulmonary embolism in unstable patients was 820 of 9810 (8.4%) with thrombolytic therapy versus 1080 of 2600 (42%) with no thrombolytic therapy ($P < .0001$). Case fatality rate attributable to pulmonary embolism in unstable patients with thrombolytic therapy plus vena cava filter was 70 of 2590 (2.7%) versus 160 of 600 (27%) with a filter alone ($P < .0001$).

CONCLUSION: In-hospital all-cause case fatality rate and case fatality rate attributable to pulmonary embolism in unstable patients was lower in those who received thrombolytic therapy. Thrombolytic therapy resulted in a lower case fatality rate than using vena cava filters alone, and the combination resulted in an even lower case fatality rate. Thrombolytic therapy in combination with a vena cava filter in unstable patients with acute pulmonary embolism seems indicated.

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KEYWORDS: Pulmonary embolism; Thrombolytic therapy; Venous thromboembolism

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Since the first clinical report of the use of a thrombolytic agent (streptokinase) in patients with pulmonary embolism by Browse and James in 1964,[1] several randomized controlled trials, beginning with the Urokinase Pulmonary Embolism Trial,[2] showed more rapid lysis of pulmonary thromboemboli with thrombolytic agents than with anticoagulants alone.[3-8] Among symptomatic patients with pulmonary embolism who were not in shock, randomized controlled trials[2,5-10] showed that case fatality rate was comparable in those treated with thrombolytic agents and those treated with anticoagulants alone. A meta-analysis of patients not in shock showed no benefit of thrombolytic agents compared with anticoagulants in terms of recurrent pulmonary embolism or death.[11]

Thrombolytic therapy would seem appropriate in patients in shock;[12] however, data are sparse and inconsistent. Among patients in shock in the Urokinase Pulmonary Em-

bolism Trial, 2-week case fatality rate among those treated with urokinase was 2 of 2 (100%) versus 1 of 1 (100%) in those treated with anticoagulants.[2] In a trial of patients with massive pulmonary embolism in shock, case fatality rate was 0 of 4 (0%) in patients randomized to streptokinase and 4 of 4 (100%) among patients randomized to heparin alone (P = .02).[13] Among hypotensive patients with pulmonary embolism in the International Cooperative Pulmonary Embolism Registry (ICOPER), 90-day case fatality rate was similar in 33 patients who received thrombolytic therapy and in 73 patients who did not (46% vs 55%).[14] Meta-analysis of 5 trials that included patients with unstable pulmonary embolism and patients who were not unstable showed a lower end point of death or recurrent pulmonary embolism in patients treated with thrombolytic agents (9.4% vs 19.0%).[11]

There are no definitive trials that prove the value of thrombolytic therapy in unstable patients with pulmonary embolism. It is extremely remote that a randomized controlled trial will be performed in the future. We therefore analyzed the database of the Nationwide Inpatient Sample to test the hypothesis that thrombolytic therapy reduces case fatality rate in unstable patients with acute pulmonary embolism.

MATERIALS AND METHODS

Unstable patients with acute pulmonary embolism discharged from short-stay hospitals throughout the United States from 1999 to 2008 and their in-hospital mortality according to the use of thrombolytic therapy were identified from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.[15]

The Nationwide Inpatient Sample contains data from 5 to 8 million hospital stays from approximately 1000 hospitals. It is designed to approximate a 20% sample of US nonfederal, short-term hospitals as defined by the American Hospital Association and is stratified according to geographic region, ownership, location, teaching status, and bed size.[3] Weights are provided to calculate national estimates. The Nationwide Inpatient Sample is drawn from those states participating in the Healthcare Cost and Utilization Project. The Nationwide Inpatient Sample contains uniform inpatient stay data collected from existing hospital discharge databases maintained by state agencies, hospital associations, and other private data organizations.[15]

> ### CLINICAL SIGNIFICANCE
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> - All-cause in-hospital case fatality rate was reduced from 47% to 15% with thrombolytic therapy in unstable patients with pulmonary embolism.
> - Death attributable to pulmonary embolism was reduced from 42% to 8% with thrombolytic therapy in unstable patients with pulmonary embolism.
> - Thrombolytic therapy resulted in a lower case fatality rate than using vena cava filters alone.
> - The combination of thrombolytic therapy and vena cava filters resulted in the lowest case fatality rate in unstable patients with pulmonary embolism.

Identification of Pulmonary Embolism

The International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes used for identification of patients with pulmonary embolism were 415.1, 634.6, 635.6, 636.6, 637.6, 638.6, and 673.2.

Primary Diagnosis of Pulmonary Embolism

Patients with a first listed diagnostic code for pulmonary embolism were considered to have a primary diagnosis, and we assumed they were admitted to the hospital because of pulmonary embolism.

Identification of Vena Cava Filter Insertion

The ICD-9-CM code used for insertion of a vena cava filter was 38.7, "Interruption of the vena cava, insertion of implant or sieve in vena cava, ligation of vena cava (inferior, superior), plication of vena cava." Since 1979, this code applies almost entirely to vena cava filters. From 1979 to 1985, the use of surgical caval interruption decreased to virtually zero.[16]

Thrombolytic Therapy

Thrombolytic therapy was identified as ICD-9-CM procedure code 99.10.

Embolectomy

Pulmonary embolectomy was identified as ICD-9-CM procedure code 38.05. Catheter embolectomy was presumed to be ICD-9-CM procedure code 39.79, endoluminal repair, other.

Definition of Unstable

Unstable was defined as having a listed code for shock (ICD-9-CM code 785.5) or ventilator dependence (ICD-9-CM code V46.1).

Comorbid Conditions

The conditions included in the Charlson comorbidity index[17] and the ICD-9-CM codes that we used to identify these conditions are shown in **Table 1**. This method of classifying comorbidity provides a simple, readily applicable, and valid method of estimating risk of death from comorbid disease.[17]

Statistical Methods

Differences in case fatality rates were assessed by chi-square and relative risk, and 95% confidence intervals (CIs)