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Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial

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Abstract. To test the efficacy of thrombolytic therapy in massive pulmonary embolism, we conducted a prospective randomized controlled trial. Eight patients were randomized to receive either 1,500,000 IU of streptokinase in 1 hour through a peripheral vein followed by heparin or heparin alone. All patients had major risk factors for deep vein thrombosis (DVT) and were considered to have high clinical suspicion for pulmonary embolism (PE). At baseline all patients had a similar degree of systemic arterial hypotension, pulmonary arterial hypertension, and right ventricular dysfunction. The time of onset of cardiogenic shock in both groups was comparable (2.25 ± 0.5 hours in the streptokinase group and 1.75 ± 0.96 hours in the heparin group). The four patients who were randomized to streptokinase improved in the first hour after treatment, survived, and in 2 years of follow-up are without pulmonary arterial hypertension. All four patients treated with heparin alone died from 1 to 3 hours after arrival at the emergency room ($p = 0.02$). Post-thrombolytic therapy the diagnosis of PE was sustained in the streptokinase group by high probability V/Q lung scans and proven DVT. A necropsy study performed in three patients in the heparin group showed massive pulmonary embolism and right ventricular myocardial infarction, without significant coronary arterial obstruction. The results indicate that thrombolytic therapy reduces the mortality rate of massive acute pulmonary embolism.

Key Words. massive pulmonary embolism, thrombolytic therapy in pulmonary embolism.

In 1977, streptokinase was approved by the FDA for the treatment of pulmonary embolism (PE; 250,000 IU/30 min and then 100,000 IU/hr/24 hr) [1]. Recently, we reported the successful use of 1,500,000 IU of streptokinase (SK) over 1 hour in one patient with massive PE and cardiogenic shock [2]. We subsequently undertook a trial of eight patients with PE who were randomized to high-dose, short-infusion streptokinase followed by heparin versus heparin alone. When all four heparin-alone patients died compared with none in the streptokinase group, we terminated the trial.

Materials and Methods

Inclusion criteria were (a) patient age ≥15 years, (b) previously healthy patients, (c) PE diagnosis sustained by high clinical suspicion (one or more major risk factors and clinical, ECG, chest x-ray, blood gas findings), (d) PE proven by high-probability V/Q lung scan [3], suggestive echocardiogram [4], or deep venous thrombosis (DVT) [5] by radiovenogram, (e) massive PE, defined as >9 obstructed segments on V/Q lung scan [6] with or without cardiogenic shock (systolic BP <90 mmHg), (f) <9 obstructed segments on V/Q lung scan but with right ventricular dysfunction and/or extensive DVT, and (g) symptoms or signs of PE within 14 days after the onset of symptoms. Exclusion criteria were (a) previous PE, (b) patients with <3 segmental defects on V/Q lung scan, with normal echocardiogram and without DVT, and (c) absolute contraindication for thrombolytic therapy: active or recent hemorrhage, intracranial disease, head trauma, neurologic or major surgery within previous 6 weeks, or any concurrent condition considered to limit survival to a few months.

The patients were randomized to streptokinase followed by heparin or to heparin alone by withdrawal of a sealed envelope from a closed box that initially contained 40 envelopes numbered consecutively from 1 to 40; even numbers were assigned to SK plus heparin and odd numbers to heparin alone. The first two patients were randomized to heparin alone, the next patient to streptokinase plus heparin, the next two to

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heparin alone, and the last three to streptokinase plus heparin.

Therapy regimen

The streptokinase group received 1,500,000 IU of SK over 1 hour by the peripheral vein, followed by a bolus of 10,000 U of heparin and then a constant infusion of 1000 u/hr of heparin titrated to a partial thromboplastin time (PTT) of 2–2.5 times control. The heparin group followed the same regimen, but without streptokinase. In the survivors of the acute phase, on the fifth day heparin was overlapped with Coumadin and was stopped on day 7. The patients were kept on Coumadin, aiming for an INR of 2.0–3.0 for 3 months or more, depending on the presence of major risk factors.

V/Q lung scans, echocardiograms, and radionuclide venograms

V/Q lung scans were performed in the anterior, posterior, lateral, and oblique views. Echocardiograms required measurements of right and left ventricular size and motion, ejection fraction, abnormal septal position, paradoxical systolic motion, and tricuspid and/or pulmonary regurgitation. Parasternal long-axis, apical four-chamber, and subcostal four-chamber views were performed. Pulmonary arterial pressure was determined with the modified Bernoulli formula. Static and dynamic venograms with 99 technetium-labeled albumin macroaggregates were performed. Variables for the two groups were analyzed using the paired Student's t test, chi-square, the two-tailed Fisher exact test, and ANOVA. All data are expressed as mean ± SD.

Results

Eight patients were enrolled, four in each group, all with massive PE and cardiogenic shock. The mortality in the streptokinase group was 0% compared with 100% ($p = 0.02$) in the heparin group. Therefore, after discussion with the ethics committee the trial was terminated.

These eight patients had similar baseline characteristics, except in time elapsed from onset of symptoms of the first event of PE before randomization, which occurred by chance (Table 1). Patients in the streptokinase group arrived at the Emergency Department from 1 to 4 hours after the onset of symptoms of PE, whereas patients in the heparin group had a first PE in other hospitals. In this first pulmonary event, they had minor PE in one, two, two and three occluded segments on V/Q lung scan, with hemodynamic stability, without any evidence of acute pulmonary arterial hypertension, and with therapeutic PTTs, respectively. They were asymptomatic and suddenly had recurrences of massive PE, with severe respiratory failure, and were transferred to our hospital at 2–4 hours after the onset of symptoms of a new event. The time that elapsed from the onset of cardiogenic shock was comparable in both groups (Table 2).

All patients had similar clinical characteristics and echocardiographic abnormalities. The patients who were randomized to receive streptokinase plus heparin improved their clinical and echocardiographic findings in the first hour after treatment (Table 1). The V/Q lung scans post-thrombolytic therapy showed three, four, four, and five segment perfusion defects, respectively, and DVT was proved. All patients in the heparin group died despite endotracheal intubation, mechanical ventilation, and Swan-Ganz catheterization (Table 2). Necropsy was performed in three patients; all had massive PE, and both macroscopically and histologically right ventricle acute myocardial infarction (RV AMI) was found; two were subendocardial and one was transmural, in all cases without significant coronary arterial obstruction. The four patients who lived were discharged in good condition. After a 2 year follow-up, all are in functional class I, without pulmonary arterial hypertension and without recurrent PE.

Discussion

We present the first randomized clinical trial that demonstrates a decreased mortality rate with thrombolysis compared with heparin alone among patients with massive PE. Because of their grave clinical condition, in the acute phase the diagnosis of PE was sustained by high clinical suspicion and only a bedside echocardiogram. Later, diagnosis of PE was confirmed by means of high-probability V/Q lung scans and proven DVT in the streptokinase group and through a high-probability V/Q lung scan in two patients of the heparin group and by necropsy in three of them. On admission, the baseline clinical and echocardiographic data showed severe right ventricular dysfunction and cardiogenic shock. However, after treatment the patients who received streptokinase plus heparin had earlier reversal of hemodynamic disturbances than patients who received only heparin, who deteriorated and died. We did not observe major or minor hemorrhagic complications, possibly due to the patients' young age, because the streptokinase was administered through a peripheral vein, and because of a diagnostic strategy that avoided vascular puncture.

In our cases, the role of echocardiography was to establish a bedside diagnosis of massive PE, to ascertain the severity of pulmonary arterial hypertension, and to document abnormalities of motion and geometry of the right ventricle. The findings in the necropsy studies have been previously reported [6] and suggest that RV AMI could cause irreversible right ventricular dysfunction and mortality. The patients who received thrombolysis had reductions in pulmonary arterial hypertension, right ventricular dysfunction, and preservation of ventricular myocardial viability.

Table 1. *Patient characteristics*

Variable	Streptokinase + heparin (n = 4)		Heparin alone (n = 4)	
Age (yr)	51 ± 22.89		46.5 ± 10.28	
Female/male	1/3		2/2	
Onset/first PE	2.50 ± 1.29 hr		34.75 ± 19.35 hr	
Onset/card shock	2.25 ± 0.50 hr		1.75 ± 0.96 hr	
Assessment of therapy	Pre	Post[a]	Pre	Post[a]
Dyspnea	3	0	4	4
Angina	4	0	4	2
S3 gallop	4	0	4	2
Card shock	4	0	4	4
RR	42 ± 3.56	20	39.50 ± 1	36.75 ± 2.36
HR	122.50 ± 9.57	82.50 ± 9.57	125 ± 17.32	117.50 ± 25
DBP	66.75 ± 4.72	94.75 ± 3.50	67.25 ± 14.5	76.75 ± 20.5
PaO_2	46 ± 9.52	65.50 ± 8.43	45 ± 10	48.25 ± 8.88
Echocardiographic findings				
RV hypokinesis	4	1	4	4
ASP	4	0	4	4
PSM	4	0	4	4
RVDR	38.50 ± 4.43	30.75 ± 5.12	40.50 ± 2.08	41 ± 2.16
PASP	97 ± 4.76	32 ± 4.08	93.75 ± 7.50	91.25 ± 10

Card = cardiogenic; RR = respiratory rate; HR = heart rate; DBP = diastolic blood pressure; RV = right ventricle; ASP = abnormal septal position; PSM = paradoxical systolic motion; RVDR = diameter ratio; PASP = pulmonary arterial systolic pressure.
[a]One hour after treatment.

Table 2. *Characteristics of the deaths in the heparin group*[a]

Age/Sex	Onset PE	Last PE before arrival to ER	Onset CS after arrival to ER	Time of death
60/M	7	2	1	24
46/F	48	3	2	72
35/F	48	2	3	20
45/M	36	4	1	32

[a]Data are given in hours.
CS = cardiogenic shock; ER = emergency room; M = male; F = female; PE = pulmonary embolism.

Rapid reversal of right ventricular failure, noted previously in rt-PA patients when compared with heparin-alone patients [7], is the likely mechanism that prevented death from acute PE. There were two limitations of this study: (1) the small sample size and (2) the gross imbalance in the onset of the first PE; however, at that moment patients in the heparin group did not have right ventricular dysfunction. The observations from this randomized, controlled clinical trial indicate that among patients with massive PE and cardiogenic shock, prompt administration of thrombolytic therapy can be lifesaving when compared with heparin alone.

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