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Regular Article

Catheter-directed ultrasound-accelerated thrombolysis for the treatment of acute pulmonary embolism

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ABSTRACT

Background: Systemic thrombolysis rapidly improves right ventricular (RV) dysfunction in patients with acute pulmonary embolism (PE) but is associated with major bleeding complications in up to 20%. The efficacy of low-dose, catheter-directed ultrasound-accelerated thrombolysis (USAT) on the reversal of RV dysfunction is unknown.

Materials and methods: We performed a retrospective analysis of 24 PE patients (60 ± 16 years) at intermediate (n = 19) or high risk (n = 5) from the East Jefferson General Hospital who were treated with USAT (mean rt-PA dose 33.5 ± 15.5 mg over 19.7 hours) and received multiplanar contrast-enhanced chest computed tomography (CT) scans at baseline and after USAT at 38 ± 14 hours. All CT measurements were performed by an independent core laboratory.

Results: The right-to-left ventricular dimension ratio (RV/LV ratio) from reconstructed CT four-chamber views at baseline of 1.33 ± 0.24 was significantly reduced to 1.00 ± 0.13 at follow-up by repeated-measures analysis of variance ($p<0.001$). The CT-angiographic pulmonary clot burden as assessed by the modified Miller score was significantly reduced from 17.8 ± 5.3 to 8.7 ± 5.1 ($p<0.001$). All patients were discharged alive, and there were no systemic bleeding complications but four major access site bleeding complications requiring transfusion and one suspected recurrent massive PE event.

Conclusions: In patients with intermediate and high risk PE, low-dose USAT rapidly reverses right ventricular dilatation and pulmonary clot burden.

Introduction

Pulmonary embolism (PE) is a potentially life-threatening condition that afflicts an estimated 600,000 patients and between 50,000 to 200,000 deaths each year in the United States [1–3]. A majority of PE patients have a benign clinical course once therapeutic levels of anticoagulation are established. However, high-risk PE involving circulatory collapse or systemic arterial hypotension is associated with an early mortality rate of approximately 50%, in part from right ventricular failure [4]. Normotensive PE patients presenting with right ventricular dilatation or dysfunction are at intermediate risk of death or recurrent venous thromboembolism [4].

Patients with high-risk PE and a low risk of bleeding should receive thrombolysis, as may patients with intermediate-risk PE [5]. In comparison to anticoagulation alone, systemic thrombolysis can reverse right ventricular dilatation within 24 hours of treatment [6,7]. Despite these effects, adverse effects including major hemorrhage (in up to 20%) and intracranial hemorrhage (in up to 3%) limit the use of thrombolysis [8]. Surgical pulmonary artery thrombectomy represents another high-risk treatment alternative, but carries a substantial risk of morbidity. Thus, there is a need for effective treatment alternatives for acute PE that facilitate the reversal of right ventricular dysfunction without causing an excess in systemic bleeding complications. The purpose of this study was to assess the hemodynamic effects of catheter-directed, ultrasound-accelerated thrombolysis (USAT) in patients with high- and intermediate-risk PE.

Materials and methods

Patients

At the East Jefferson General Hospital, catheter-directed thrombolysis (CDT) is a standard procedure for patients with high and

Abbreviations: RV, right ventricular; PE, pulmonary embolism; USAT, ultrasound accelerated thrombolysis; CDT, catheter-directed thrombolysis; rt-PA, recombinant tissue plasminogen activator; CT, computed tomography; RV/LV ratio, right-to-left ventricular dimension ratio; LOS, length-of-stay; IDDC, intelligent drug delivery catheter; MSD, microSonic device.

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intermediate-risk PE. This report describes the treatment of 27 consecutive patients with high and intermediate-risk PE using combined treatment with catheter-directed USAT (EkoSonic Endovascular System, EKOS Corporation; Bothell; WA) and rt-PA (Genentech; San Francisco, CA) between February 2009 and July 2010. Patients were treated if they fulfilled all of the following criteria: a) dyspnea, hypoxia, or hemodynamic instability, b) evidence of PE by multi-detector contrast-enhanced computed tomography (CT), and c) right ventricular dysfunction by echocardiography or right-to-left ventricular dimension ratio >0.9 by CT. Written informed consent for catheter-directed thrombolysis was obtained in all patients prior to the procedure.

Medical records were reviewed and clinical data including symptoms, risk factors for venous thromboembolism, treatment details, and length-of-stay (LOS) were recorded. Telephone follow-up was obtained in all 27 patients at 269 ± 139 days (minimum 64 days; maximum 584 days) following hospital discharge. Three patients were excluded from the analysis because no post-treatment contrast-enhanced CT was available; two were alive at follow-up and one had died from cancer. Retrospective data collection for this observational experience was approved by the local Institutional Review Board (EJ - TE-1002).

EkoSonic device

The EKOS EkoSonic® Endovascular system (Fig. 1) delivers low-intensity ultrasound for the purpose of facilitated thrombolysis using low-dose fibrinolytic therapy. The ultrasound disaggregates fibrin strands, increases permeability of the clot, and disperses the fibrinolytic drug into clot through acoustic microstreaming effects [9,10].

The EkoSonic Endovascular System includes an Intelligent Drug Delivery Catheter (IDDC), MicroSonic Device (MSD) containing a series of miniature ultrasound transducers positioned along the treatment zone, and a Control Unit. The IDDC is a 5.2Fr multi-lumen sideport infusion catheter, with infusion lengths ranging from 6 to 50 cm, which accommodates the coaxial 0.035" MSD to deliver uniform radial ultrasound energy (2.2 MHz) to the entire infusion zone with simultaneous rt-PA infusion. The Control Unit continuously monitors treatment zone temperature measured by the IDDC's thermocouples and automatically adjusts delivered ultrasound power to optimize thrombolysis. The EkoSonic System has been previously cleared by the US FDA for the infusion of solutions into the pulmonary arteries (K073166, April 22, 2008). Intravenous infusion of rt-PA is the approved route of administration for rt-PA.

Treatment regimen

All patients received low molecular weight heparin (Lovenox, Sanofi-Aventis, Bridgewater, NJ) using a standard weight-based algorithm (1 mg/kg/12 hours, subcutaneous) prior to, during, and after USAT treatment. The placement of the EkoSonic Endovascular System was performed in the cardiac catheterization laboratory. Venous access was obtained via the common femoral vein. In the first 14 patients, venous access was maintained with a 6 Fr introducer sheath (Boston Scientific; Natick, MA) and both right and left femoral veins were accessed in patients requiring placement of two EkoSonic devices. Beginning in February 2010 a 10 Fr dual lumen introducer sheath (FastCath Duo; St. Jude Medical; St. Paul, MN) was used requiring only one venous access site in patients receiving two EkoSonic devices. Following placement of the introducer sheath, a 260 cm guide wire (Cook, Inc.; Bloomington, IN) and 5 Fr angled pigtail catheter (Boston Scientific; Natick, MA) were advanced into the desired location in the pulmonary artery. The pigtail catheter was then removed and the EkoSonic IDDC was advanced over the guide wire until the treatment zone of the catheter was in the correct location directly within the embolus. The guide wire was then removed and replaced by the MSD containing the ultrasound transducers. Heparinized saline was infused through the central lumen of the IDDC and ultrasound delivery was initiated. Patients were transported to the Intensive Care Unit while rt-PA was being infused with simultaneous ultrasound delivery. Patients treated early in the series received rt-PA and ultrasound for approximately 24 hours. Infusion was discontinued when the cardiac catheterization laboratory was available for follow-up or if an adverse event occurred. In the last 7 patients, upon reaching maximum total dose of 20 mg rt-PA at 12 hours, the infusion and ultrasound were turned off and the EkoSonic devices were removed at bedside. Follow-up CT scans were performed after completion of treatment and removal of the EkoSonic Devices at 38 ± 14 hours (minimum 16 hours, maximum 79 hours).

Definitions and endpoints

Technical success was defined as successful placement of the EkoSonic device and initiation of the rt-PA infusion with simultaneous ultrasound delivery. The change from baseline to follow-up of the right-to-left ventricular dimension ratio (RV/LV ratio) was obtained

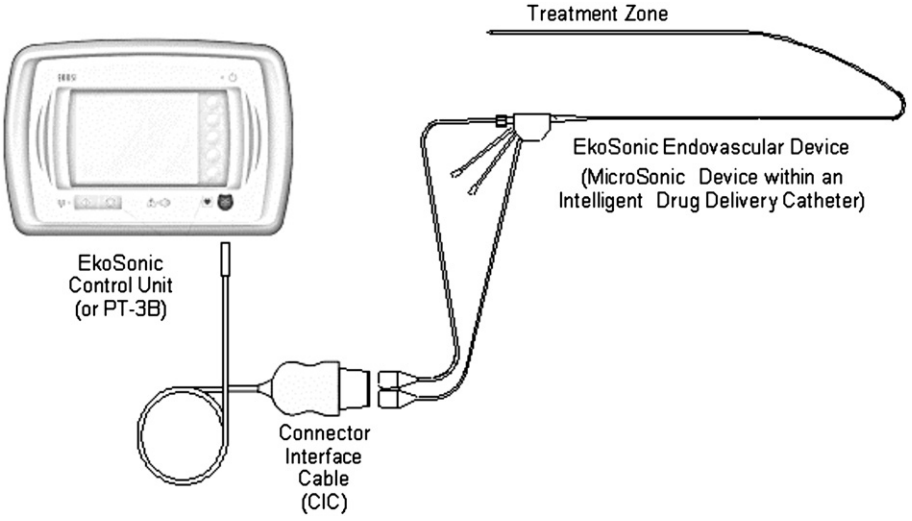

Fig. 1. EKOS EkoSonic® Endovascular system.