Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism


Acute massive pulmonary embolism (PE) is a life-threatening condition that requires prompt and aggressive interventions, including anticoagulation, catheter-directed thrombolysis (CDT), mechanical thrombectomy, or surgical thromboembolectomy. The aim of this study was to evaluate the treatment outcome in patients with massive PE who were treated with either ultrasound-accelerated thrombolysis using the EkoSonic Endovascular System (EKOS) or CDT intervention. During a recent 10-year period, the clinical records of all patients with massive PE undergoing catheter-directed interventions were evaluated. Patients were divided into two treatment groups: EKOS versus CDT interventions. Comparisons were made with regard to the treatment outcome between the two groups.

Twenty-five patients underwent 33 catheter-directed interventions for massive PE during the study period. Among them, EKOS or CDT was performed in 15 (45%) and 18 (55%) procedures, respectively. In the EKOS group, complete thrombus removal was achieved in 100% cases. In the CDT cohort, complete or partial thrombus removal was accomplished in 7 (50%) and 2 (14%) cases, respectively. Comparing treatment success based on thrombus removal, EKOS treatment resulted in an improved treatment outcome compared with the CDT group (p < .02). The mean time of thrombolysis in EKOS and CDT group was 17.4 ± 5.23 and 25.3 ± 7.35 hours, respectively (p = .03). The mortality rate in the EKOS and CDT group was 9.1% and 14.2%, respectively (not significant). Treatment-related hemorrhagic complication rates in the EKOS and CDT group were 0% and 21.4%, respectively (p = .02). A significant reduction in Miller scores was noted in both groups following catheter-based interventions. No significant difference in relative Miller score improvement was observed between groups. Ultrasound-accelerated thrombolysis using the EkoSonic system is an effective treatment modality in patients with acute massive PE. When compared with CDT, this treatment modality provides similar treatment efficacy with reduced thrombolytic infusion time and treatment-related complications.

Key words: catheter-directed thrombolysis, pulmonary embolism, ultrasound-accelerated thrombolysis

Pulmonary embolism (PE) is a highly lethal condition that is responsible for 150,000 to 200,000 deaths every year and has been estimated to affect more than 600,000 patients annually in the United States.¹,² The mortality rate in the first 3 months following the diagnosis of PE has been shown to range from 15 to 18%.³,⁴ Massive PE, in contrast, is characterized by circulatory collapse or hemodynamic instability, which is associated with a threefold increased inpatient mortality compared with those patients without hemodynamic instability.⁵,⁶ Although the lethality data of this devastating condition are comparable to those of acute myocardial infarction, the overall mortality rates associated with PE have not improved significantly over the past three decades.⁷,⁸

The ideal treatment strategies for patients with massive PE have been a subject of controversy as no randomized controlled trials exist to support an optimal therapeutic modality. In fact, the only randomized controlled trial in patients with massive PE that compared systemic streptokinase thrombolytic therapy versus heparin treatment en-
rolled only eight patients. The trial was stopped owing to ethical concerns because all four patients receiving thrombolytic therapy survived, whereas those receiving heparin suffered fatal outcomes. The use of thrombolytic agents in acute PE was first reported more than three decades ago. Since then, clinical studies, experimental models, and case series have consistently demonstrated the efficacious outcome of catheter-directed thrombolytic (CDT) therapy on hemodynamic and angiographic variables of patients with symptomatic or massive PE. This treatment strategy has been accepted beyond a reasonable doubt as thrombolytic therapy is superior to conventional systemic anticoagulation with regard to early resolution of pulmonary artery embolism and restoration of right ventricular (RV) function.

CDT therapy enables a high concentration of thrombolytic agents to be infused directly into the thrombus, resulting in shorter infusion times and reduced doses of the thrombolytic drug needed for thrombus resolution, which, theoretically, decreases the risk of hemorrhagic complications compared with systemic thrombolysis. In recent years, interest has risen in a variety of endovascular strategies based on catheter-based technologies for thrombus removal in patients with massive PE. Various mechanical devices based on fragmentation or rheolytic thrombectomy principles have shown clinical efficacy in radiographic thrombus resolution as well as symptomatic improvement in patients with PE. The enthusiasm of these catheter-based mechanical thrombectomy interventions has also been hampered by reports of complications such as bradyarrhythmias, fragmentation-induced embolization, vessel wall perforation, valvular damage, and paradoxical circulatory collapse following catheter-based PE interventions. The EkoSonic Endovascular System (EKOS, Bothell, WA) is an ultrasound-accelerated CDT treatment strategy that emits low-intensity, high-frequency ultrasound that dissociates fibrin strands without causing thrombus fragmentation. When the ultrasound energy is delivered concomitantly with CDT infusion, the acoustic energy enhances thrombolytic penetration into the thrombus and increases thrombus surface area, which allows greater fibrinolytic drug binding to the thrombus surface receptors. The efficacy of this ultrasound-accelerated thrombolytic therapy has been demonstrated in experimental investigation as well as clinical studies of deep venous thrombosis (DVT) and embolic stroke. The efficacy of this treatment strategy was recently investigated in the treatment of massive PE. The primary objective of this study was to evaluate the clinical efficacy of ultrasound-accelerated thrombolytic therapy in patients with massive PE. The clinical outcome of this ultrasound-assisted treatment strategy was compared with patient cohorts who underwent CDT therapy. Our secondary aim in this study was to highlight the efficacy of this treatment modality so that health care providers can incorporate this therapeutic strategy in the overall armamentarium of endovascular treatment of PE.

Patients and Methods

Patients

From May 1999 to August 2009, the clinical records of all patients who were diagnosed with PE and underwent catheter-based interventions were analyzed. For the purpose of this study, specific attention was focused on patients with massive PE who underwent two types of catheter-based PE interventions, including ultrasound-accelerated thrombolytic therapy using the EkoSonic Endovascular System (EKOS group) or CDT therapy (CDT group). Catheter-based interventions were performed by either interventional radiologists or vascular surgeons. Two thrombolytic agents were used for CDT infusion, which included urokinase (Abbott Laboratories, North Chicago, IL, or ImaRx Therapeutics, Tucson, AZ), and tissue plasminogen activator (tPA) (Activase, Genentech, South San Francisco, CA). Indications for pulmonary arterial thrombolytic therapy included patients with massive PE who had (a) shortness of breath, hypoxia, or hemodynamic instability; (b) a dilated right ventricle at echocardiography; and (c) electrocardiographic findings of the RV strain. Hemodynamic instability was defined as systolic arterial pressure less than 90 mm Hg or a drop in systolic arterial pressure of at least 40 mm Hg for at least 15 minutes. The diagnosis of massive PE was based on a variety of imaging and clinical modalities, which included computed tomographic (CT) angiography, ventilation-perfusion scintigraphy, echocardiography, and physical examination.

EkoSonic Endovascular System

Ultrasound-assisted CDT was performed with the EkoSonic Endovascular System. This is a 5.2F multilumen side-port infusion catheter with infusion lengths of 6 to 50 cm depending on the length of the occlusion. The drug delivery catheter was navigated over a 0.035-inch guidewire so that the treatment zone traversed the entire clot and
the tip exited the thrombus. After final positioning, the guidewire was exchanged for a matching ultrasound core wire containing a series of ultrasound transducer elements (2.2 MHz, 0.45 W), which are distributed approximately 1.0 cm apart along its leading tip to evenly deliver ultrasound energy radially along the coaxial infusion zone (Figure 1). A control unit provides continuously monitored variables, including temperature and ultrasound energy power output in the treatment zone, by means of thermocouples incorporated in the catheter and automatically adjusts power to optimize lysis of the intravascular thrombosis. The acoustic streaming energy dissociates the fibrin and increases the fibrin porosity without causing distal embolization, which also facilitates the penetration of thrombolytic agent into the thrombus for receptor binding.

**Techniques of Ultrasound-Accelerated CDT versus CDT**

The technique of performing ultrasound-accelerated thrombolytic therapy involved the placement of an EkoSonic catheter in the pulmonary artery (EKOS group), whereas a conventional multilumen thrombolytic infusion catheter (UniFuse thrombolytic infusion catheter, Angio- dynamics, Queensbury, NY) was used in the conventional CDT treatment group. In both treatment groups, an initial groin access was obtained in the femoral vein using a micropuncture needle and catheter (Boston Scientific, Natick, MA). Following the placement of a 6F introducer sheath (Boston Scientific), pulmonary angiography was performed by using a 6F MONT-1 pulmonary angiographic catheter (Cook, Bloomington, IN) (Figure 2). Bilateral femoral accesses were obtained in patients whose PE occurred in bilateral pulmonary vasculature. Once the location of a pulmonary arterial thrombus was identified angiographically, the angiographic catheters were exchanged for an EkoSonic infusion catheter, which was navigated over a 0.035-inch angled glidewire (Terumo, Somerset, NJ), such that the distal EkoSonic catheter tip was positioned at the distal edge of the thrombus under fluoroscopy. The guidewire was next exchanged for the corresponding ultrasound transducer core wire, which is connected to the control unit for ultrasound energy transmission. Appropriate thrombolytic agent and saline coolant solution at 45 cc per hour were delivered via the designated infusion lumens in the EkoSonic catheter. Heparin infusion was maintained at 400 IU per hour via the side port of the groin introducer sheath. Ultrasound energy was delivered concomitantly
with infusion of the thrombolytic agent via the EkoSonic catheter.

**Angiographic Analysis Based on the Miller Index**

Pre- and postintervention pulmonary angiography was analyzed by a blinded interventionalist for evidence of thrombus removal based on the published criteria as reported by Miller and colleagues.\(^3\) Briefly, the obstruction index was calculated based on the following formula: seven major branches were identified in the left pulmonary artery (two in the upper lobe, two in the lingual, and three in the lower lobe), and nine major segmental branches were identified in the right pulmonary artery (three in the upper lobe, two in the middle lobe, and four in the lower lobe). The presence of filling defects (emboli) in any of these branches was scored 1 point per each segment involved, thus leading to an overall obstruction score ranging from 0 (best) to 16.

**Figure 2.** *A.* Selective angiography of the left main pulmonary artery demonstrated a perfusion defect caused by pulmonary embolism in the inferior branch of the left pulmonary artery (*arrow*). *B.* Successful treatment of ultrasound-accelerated thrombolytic therapy restored pulmonary arterial flow of the left dorsal inferior pulmonary artery with improved perfusion of the pulmonary parenchyma.

**Figure 3.** *A.* Helical computed tomographic (CT) angiogram showing emboli in bilateral pulmonary arteries with large thrombus in the left main pulmonary artery (*short arrow*) and multiple thrombi in the right main pulmonary artery (*long arrow*) prior to ultrasound-accelerated thrombolytic therapy. *B.* Follow-up CT angiography performed 5 days following successful thrombolytic therapy using the EkoSonic device demonstrated complete resolution of bilateral pulmonary embolism.
performed. Statistical analysis was performed by means of and duration of therapy between the treatment groups was discretion of the treating physicians.

patients with documented lower extremity DVT or at the least 50%. Inferior vena cava (IVC) filters were inserted in (c) a decrease in the mean pulmonary arterial pressure of at clinical symptoms despite the presence of residual clot, or no change in clot burden after 24 hours, (b) resolution of lytic therapy were based on the following conditions: (a) ent (Figure 3). The criteria used for stopping thrombo-

was performed whenever clinical indications were pres-

formed 12 to 48 hours after the initiation of catheter-based interventions to determine the need to either continue or stop thrombolysis. Helical CT angiography of the chest was performed whenever clinical indications were present (Figure 3). The criteria used for stopping thrombolysis therapy were based on the following conditions: (a) no change in clot burden after 24 hours, (b) resolution of clinical symptoms despite the presence of residual clot, or (c) a decrease in the mean pulmonary arterial pressure of at least 50%. Inferior vena cava (IVC) filters were inserted in patients with documented lower extremity DVT or at the discretion of the treating physicians.

Statistical comparison of the relative MS improvement and duration of therapy between the treatment groups was performed. Statistical analysis was performed by means of the Fisher exact test or Pearson chi-square test in categorical variables. The Wilcoxon rank sum test was used to test for differences in continuous variables. All statistical analyses were performed using the SAS statistical software program (SAS Institute, Cary, NC). All values were expressed as mean ± SEM. Statistical significance was accepted with a $p$ value of less than .05

**Results**

During this study period, 25 patients who underwent 33 catheter-directed interventions for massive PE were included in the study. Among them, 11 patients with massive PE underwent EkoSonic ultrasound-accelerated thrombolytic therapy for 15 lesions (EKOS group). Fourteen patients with 18 PE lesions received CDT infusion without adjunctive ultrasound therapy (CDT group). Successful catheter-based interventions were initiated as the infusion catheter was positioned appropriately within the thrombus in all patients in both groups. Pertinent clinical variables and demographic information are displayed in Table 1.

In the EKOS group, tPA was used in all patients with a mean tPA dose rate of 0.86 ± 0.16 mg/h for a mean total tPA dose of 17.2 ± 2.36 mg (range 8–28 mg). The mean infusion time was 17.4 ± 5.23 hours (range 13–38 hours). There were no hemorrhagic complications in this patient group. The preintervention MS was 18.65 ± 3.25, which decreased to a postintervention MS level of 5.84 ± 1.57 (Table 2). The only fatality (9.1%) occurred in a 63-year-old male who was found unconscious prior to hospital admission. A massive PE was diagnosed following aggressive resuscitation including mechanical ventilatory support and pressor agent for blood pressure support. He expired 7 hours following EKOS treatment owing to multiorgan system failure. Complete thrombus removal was achieved in all surviving patients (100%). All patients received a G2 retrievable IVC filter (Bard, Tempe, AZ), and seven of them subsequently underwent successful IVC filter retrieval at a mean period of 7.3 ± 1.6 months. Three patients had underlying hypercoagulable conditions and decided to keep IVC filters permanently. All patients were compliant on long-term oral anticoagulation therapy with warfarin. There were no recurrent PE episodes during the follow-up period.

In the CDT group, 5 patients received urokinase and 10 patients received tPA as thrombolytic agents. The mean infusion time was 26.7 ± 8.64 hours (range 14–46 hours). The mean tPA dose rate was 0.93 ± 0.22 mg/h, for a mean total tPA dose of 25.43 ± 5.27 mg (range 16–45 mg). For
those who received urokinase thrombolytic therapy, the mean starting dose was 60,000 U/h, which was increased at 6 hours to a mean dose of 90,000 U/h. The mean total urokinase dose was 2.04 ± 0.56 million units (range 1.65–2.87 million units) delivered over a mean period of 25.3 ± 7.35 hours (range 17–39 hours). Complete thrombus resolution was achieved in seven patients (50%), whereas partial thrombolysis was achieved in two patients (14.3%). Comparing treatment success based on thrombus removal, the EKOS group had an improved treatment success compared with the CDT group (p < .02). The preintervention MS was 17.29 ± 3.86, which was decreased to 7.38 ± 2.26 following CDT therapy (see Table 2). Two patients suffered fatal outcomes (14.3%), which occurred in a 56-year-old male patient who succumbed to cardiac arrest and profound acidosis 2 hours following the initiation of thrombolytic infusion. The other fatality occurred in a 59-year-old female who had severe right heart failure and expired 13 hours following the initiation of thrombolytic therapy. There were three major bleeding complications (21.4%), which included two groin hematomas and one retroperitoneal hematoma. All bleeding complications were treated nonsurgically with immediate cessation of thrombolytic therapy and blood product transfusion. Only four patients received IVC filter placement, and none were retrieved. All surviving patients were compliant on long-term oral anticoagulation therapy with warfarin without recurrent PE episodes during the follow-up period.

Comparative analysis between the two treatment groups showed that the EKOS group had a higher treatment success rate (p < .02) and a lower complication rate (p = .02) compared with the CDT cohorts. Specifically related to the tPA dosage and infusion time, there was a reduction in the tPA dosage and infusion time in the EKOS group when compared with the CDT group (p < .001). The MSs were statistically significant in both the EKOS and the CDT group following respective interventions (p < .002). No significant difference in relative MS improvement was observed between groups.

**Discussion**

Massive PE is a life-threatening condition associated with a high incidence of fatalities comparable to that of acute myocardial infarction. Its clinical course can vary from sudden death to prolonged hospitalization with eventual mortality or lifelong morbidity related to cardiopulmonary dysfunction. Hypotension, cardiogenic shock, and RV dysfunction are the primary criteria for defining massive PE. Systemic hypotension is defined as a systolic arterial pressure < 90 mm Hg or a drop in systolic arterial pressure of at least 40 mm Hg for at least 15 minutes. Shock is defined by tissue hypoperfusion and hypoxia, including oliguria, cool and clammy extremities, or altered mental status. The presence of shock increases the mortality rate by three- to sevenfold. Acute RV dysfunction is manifested by physical findings such as distended neck veins, a parasternal heave, and a tricuspid regurgitation murmur. This diagnosis can also be supported by echocardiographic findings, which include increased RV pressure, with RV midwall hypokinesis and apical hyperkinesis. Despite a common awareness regarding the high risk of fatality of massive PE, the ideal treatment strategy for this condition remains a subject of debate as no randomized trials have

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Table 1. Baseline Epidemiologic and Clinical Data in the EKOS and CDT Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>EKOS Therapy, n (%)</th>
<th>CDT Therapy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11 (45)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>No. of PE lesions</td>
<td>15 (68)</td>
<td>18 (71)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>59 ± 17</td>
<td>62 ± 18</td>
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<tr>
<td>Male</td>
<td>5 (45)</td>
<td>7 (50)</td>
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<tr>
<td>Risk factor for pulmonary embolism</td>
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<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 (9)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>3 (27)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Trauma/fracture</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Immobilization</td>
<td>1 (9)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 (18)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Active smoking</td>
<td>4 (36)</td>
<td>2 (14)</td>
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<tr>
<td>Use of oral contraceptive</td>
<td>3 (27)</td>
<td>2 (14)</td>
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<td>Autoimmune etiology</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Unclear cause</td>
<td>2 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Clinical presentation/symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock/hypotension</td>
<td>2 (18)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>4 (36)</td>
<td>4 (28)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (2)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (9)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (73)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Right ventricular dysfunction</td>
<td>5 (45)</td>
<td>8 (57)</td>
</tr>
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</table>

CDT = catheter-directed thrombolysis; DVT = deep venous thrombosis; EKOS = EkoSonic Endovascular System; PE = pulmonary embolism.
proven an efficacious interventional or surgical therapeutic modality. Our study is notable because it represents the first clinical study comparing the treatment outcomes of two well-described thrombolytic strategies for intravascular thrombosis in patients with massive PE. This study demonstrated the equivalent clinical efficacy with reduced thrombolytic treatment duration and hemorrhagic complications in the ultrasound-accelerated thrombolytic group compared with the CDT cohorts.

A variety of treatment modalities have been used in patients with massive PE, which include systemic anticoagulation, CDT, surgical pulmonary embolectomy, and percutaneous mechanical thrombectomy.1,7,12,15,20,25,32 Although anticoagulation with unfractionated or low-molecular-weight heparin followed by long-term warfarin therapy is widely regarded as the gold standard, this treatment does not remove thrombus burden or restore vascular flow. Prior to the adoption of catheter-based interventional technologies, operative pulmonary thromboembolectomy was the only therapeutic modality in removing pulmonary thrombus in patients with hemodynamic instability. Although this operative treatment is rapidly effective in removing the occlusive PE, it is associated with a high incidence of operative morbidity and mortality, particularly in patients with compromised cardiopulmonary functions.33,34

CDT is indicated for patients with massive PE as evidenced by shock, hypotension, or other evidence of cardiopulmonary compromise attributed to massive PE.3,35–37 However, the time necessary to achieve a clinical response with thrombolytic agents such as alteplase or urokinase can vary from 4 to 46 hours, depending on the thrombus chronicity or fibrin composition.38 Although intravenous thrombolytic therapy was shown nearly two decades ago to be equally effective as CDT in the main pulmonary artery,39 most researchers would agree with the utility of catheter-based thrombolysis in massive PE based on cumulative literature support and clinical experience, which demonstrates the rapid efficacy of thrombus removal in peripheral vascular thrombosis and dialysis access graft management.40–42 Various in vitro and experimental animal models have similarly supported the therapeutic benefits and thrombolytic efficacy in PE.43,44

The concept of using an ultrasound-accelerated thrombolytic therapy in the treatment of PE was recently discussed by Chamsuddin and colleagues, who reported successful resolution of 10 patients with massive PE.40 In that multicenter clinical series, complete or near-complete thrombus removal was achieved in 94% of patients, where-

<table>
<thead>
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<tr>
<td><strong>Variable</strong></td>
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<td>No. of patients</td>
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<td>Mean age (yr)</td>
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<tr>
<td>Complete thrombolysis</td>
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<tr>
<td>Partial thrombolysis</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>Hemorrhagic complications</td>
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<tr>
<td>Thrombolytic dosage (urokinase, U × 10⁶)</td>
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<tr>
<td>Thrombolytic dose rate (tPA, mg/hr)</td>
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<tr>
<td>Thrombolytic dose (tPA, mg)</td>
</tr>
<tr>
<td>Thrombolytic infusion (hrs)</td>
</tr>
<tr>
<td>Preintervention Miller score</td>
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<tr>
<td>Postintervention Miller score</td>
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<tr>
<td>Relative Miller score improvement</td>
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</table>

CDT = catheter-directed thrombolysis; EKOS = EkoSonic Endovascular System; NA = not available; NS = not significant; PE = pulmonary embolism; tPA = tissue plasminogen activator.

* Comparison of pre- and postintervention Miller score within the EKOS group showed a significant difference with p < .002.
† Comparison or pre- and postintervention Miller score within the CDT group showed a significant difference with p < .002.
as partial thrombolysis was accomplished in 6% of patients. The mean treatment duration was 24 hours, and no patients suffered any hemorrhagic sequelae. The findings from Chamsuddin and colleagues’ series were similar to our experience using ultrasound-accelerated thrombolytic therapy. We noted that there were no hemorrhagic complications in the EKOS group, whereas conventional CDT cohorts experienced a hemorrhagic complication rate of 21.4%. We also were able to achieve similar clinical efficacy with less thrombolytic dosage and shorter infusion time, which undoubtedly lessened the bleeding complications.

Adjunctive endovascular treatments were common in our patients. All patients in the ultrasound treatment group received retrievable IVC filter placement, whereas 29% of patients in the CDT group received IVC filter placement for prevention of recurrent PE. Seven (63%) patients who received retrieved IVC filters in the EKOS group had undergone subsequent IVC filter retrieval with 100% technical success. In contrast, no patients in the CDT group who received IVC filter placement underwent filter retrieval. This was due in part to the fact that no retrieval filters were available during the study period when CDT therapy was conducted. All patients who were available for follow-up were placed on long-term oral warfarin therapy. There were no episodes of recurrent PE in our patients, even in those who underwent IVC filter retrieval following thrombolytic therapy.

Ultrasound-accelerated CDT augments the fibrinolytic process by using a high-frequency and low-intensity ultrasound energy to facilitate the dissociation of fibrin strands, which enhances the penetration of thrombolytic agents into the thrombus. The effect of ultrasound on small gas bubbles in the thrombus facilitates transport of activators and plasminogen to their target sites on fibrin molecules, which consequently increased the exposed surface area of thrombus to enable thrombolytic drug interaction. As a result, ultrasound-accelerated CDT decreases the amount of thrombolytic agents and infusion time necessary for complete thrombus resolution, which, theoretically, lowers the incidence of hemorrhagic complications.

Although several studies have reported the safety and efficacy of various catheter-based interventional techniques in patients with massive PE, including mechanical thrombectomy using embolus fragmentation devices or a rheolytic thrombectomy system, ultrasound-accelerated CDT represents a promising and exciting technology that has several advantages over mechanical thrombectomy techniques. The EkoSonic system received clearance from the Food and Drug Administration for infusion of solutions into the pulmonary arteries. Its high-frequency and lower-intensity ultrasound wave has been widely used in various medical applications and exerts no thrombolytic effects on its own. By combining the ultrasound energy and thrombolytic drugs, numerous preclinical testing and animal evaluations have demonstrated accelerated thrombolytic efficacy with lower thrombolytic dosage requirements. Additionally, common drawbacks regarding mechanical devices based on fragmentation or rheolytic thrombectomy mechanisms, such as vessel wall injury, valvular damage, and pulmonary embolization owing to direct vessel wall contact or thrombus embolization, are less likely to occur with ultrasound-accelerated thrombolytic therapy.

The benefit of using ultrasound-accelerated thrombolytic therapy has similarly been analyzed in the treatment of symptomatic iliofemoral DVT. Parikh and colleagues recently reported a series of 53 cases of DVT treated with ultrasound-accelerated thrombolysis with a remarkable treatment success of 91%. These authors reported a hemorrhagic complication rate of 3.8%, which occurred in two patients with groin-related hematoma, whereas no patients suffered an intracranial or retroperitoneal hemorrhage. This was in sharp contrast to the conventional CDT in which higher thrombolytic dosage and infusion time are often associated with a higher risk of bleeding complications. As reported in the National Venous Registry, which was a multicenter study using CDT therapy in 287 patients with symptomatic DVT, Mewissen and colleagues reported a major bleeding complication rate of 11%. Conventional DVT treatment using unfractionated or lower-molecular-weight heparin followed by oral warfarin therapy is associated with relatively low hemorrhagic rates, which ranged from 0.8 to 3.2%. Ultrasound-accelerated thrombolysis provided low major bleeding rates comparable to those of anticoagulation therapy, with the added benefit of removing thrombus burden, thereby reducing the future risk of postthrombotic syndrome. This ultrasound-accelerated CDT has similarly demonstrated clinical efficacy in removing thrombotic burden and restoring flow in patients with
Importantly, the adjunctive presence of ultrasound wave facilitates the fibrinolytic process and reduces the thrombolytic duration and dosage that contributed to the lower hemorrhagic complication rates.

There are undoubtedly numerous limitations in our study. The number of patients in each study group is admittedly small, and the length of follow-up remains limited. Additionally, the retrospective nature of this study design clearly may encompass a certain degree of patient and physician selection bias. This is particularly pertinent because nearly all CDT therapies were performed during the early phase of the study period by interventional radiologists, when percutaneous PE thrombectomy or ultrasound-accelerated technologies were not available. The subsequent availability of ultrasound-accelerated thrombolytic technology has transformed our treatment approach in patients with massive PE. Additionally, all ultrasound-accelerated CDT therapies were performed by vascular surgeons either in an endovascular operating room or catheter laboratory. The routine use of retrieval IVC filter by vascular surgeons in ultrasound-accelerated thrombolytic therapy was also in sharp contrast to the sparing placement of IVC filters by interventional radiologists in our study. Although we do not believe interventions performed by different physician specialties or procedural location would impact on the treatment outcome, this disparity in practice pattern nonetheless may be a confounding variable in the outcome analysis. A large-scale prospective study will unquestionably provide further insight regarding the clinical efficacy of ultrasound-accelerated thrombolytic therapy in patients with massive PE.

In summary, our study illustrates the beneficial role of ultrasound-accelerated thrombolytic therapy using the EkoSonic system. The clinical efficacy of this promising treatment strategy compared favorably with the CDT therapy. Importantly, our study showed a higher treatment success rate with significant reduction in thrombolytic duration, thrombolytic dosage, and hemorrhagic complications using the ultrasound-accelerated thrombolytic therapy. Additional clinical studies will be necessary to further validate the benefit and corroborate our results with this ultrasound-accelerated thrombolytic therapy in patients with massive PE.

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