Catheter-directed Thrombolysis for Severe Pulmonary Embolism in Pediatric Patients

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Background: Catheter-directed thrombolytic (CDT) therapies for severe pulmonary embolism (PE) have been shown to be effective and safe when compared with systemic thrombolysis in adults. Pediatric studies assessing efficacy and safety of CDT for PE are lacking. Hence, our aim was to review CDT as a therapy for pediatric PE.

Methods: We retrospectively reviewed charts of patients aged < 18 years, who underwent CDT for main or major branch pulmonary artery occlusion associated with hypotension or right ventricular dysfunction secondary to PE during a 3-year period, in our tertiary care academic Pediatric Intensive Care Unit.

Results: Six CDT interventions were performed on 5 patients with PE (median age: 16.5 years). All patients presented with chest pain and dyspnea. The predisposing factors for thrombogenesis differed in all patients, and all had multiple risk factors. Five of six procedures (83%) were accompanied by ultrasound agitation with EKOS endowave infusion system (ultrasound-accelerated CDT [UCDT]), whereas 1 had CDT without ultrasound agitation. Complete resolution of PE occurred in 4 instances (67%) at 24 hr, whereas in 2 cases (33%), there was partial resolution. One patient with complete resolution underwent another successful UCDT after 4 months for recurrence. Clinical parameters (heart rate, respiratory rate, blood pressure, and oxygen saturations) and echocardiographic findings improved after treatment in all the patients. Median duration of hospital stay was 9 days with no mortality and treatment-related complications. All patients were discharged with long-term anticoagulation.

Conclusions: Our case series is the first that describes CDT/UCDT as an effective and safe therapy for pediatric patients with severe PE. CDT is known to accelerate fibrinolysis via focused delivery of thrombolytic agent to the thrombus site. For carefully selected patients, CDT/UCDT provides a useful treatment option for severe PE irrespective of the etiology, predisposing conditions, and associated comorbidities.

Pulmonary embolism (PE) in children is a potentially lethal condition and yet is a vastly understudied arena. Autopsy studies show a higher prevalence (0.7–4%) of PE compared with medical database registries (0.9 per 100,000 admissions) suggesting that this condition is often clinically underrecognized.1,2 A more recent study from a tertiary emergency department in the United States...
estimates the incidence of new PE at 2.1 per 100,000 emergency room visits. As a manifestation of venous thromboembolic disease, the incidence of pediatric PE continues to rise as successful management of previously untreatable malignancies, complex congenital cardiac conditions, and usage of central venous catheters increases. Mortality of pediatric PE remains high at 10%, thus emphasizing the urgent need to appropriately diagnose and treat this condition.

Validated clinical prediction scores and risk stratification guidelines exist for adult PE. The presence of hypotension or shock signifies massive PE, whereas occurrence of right ventricular strain or hypokinesis without hemodynamic instability is classified as submassive PE. Rapid diagnosis and severity categorization facilitate prompt initiation of optimal treatment strategy that may include cardiorespiratory support, systemic anticoagulation, catheter-directed thrombolysis, systemic thrombolysis, and/or surgical embolectomy. Systemic thrombolysis and embolectomy are effective at thrombus resolution but are associated with significant hemorrhagic complications. Novel techniques such as ultrasound-accelerated CDT (UCDT) have been shown to achieve faster and more complete clot resolution with lesser complications than CDT alone in adults. However, pediatric studies assessing efficacy and safety of CDT or UCDT for PE are lacking, and hence, exploring the potential of these modalities in pediatrics was the focus of our study.

We describe here a case series of critically ill pediatric patients treated with CDT or UCDT for PE at our institution.

MATERIALS AND METHODS

Setting

We conducted a retrospective study during a 3-year period (December 2009–December 2012) after approval from the Institutional Review Board of Baylor College of Medicine. In pediatric patients aged <18 years, treated at Texas Children’s Hospital, Houston, TX with CDT or UCDT for submassive or massive PE, etiologic factors for PE and clinical parameters were reviewed.

Intervention

The indication for CDT was massive or submassive PE as defined by the presence of either hypotension or severe right ventricular (RV) dysfunction in the setting of complete occlusion of the main or major branch pulmonary arteries (PAs). RV function and strain were determined by preintervention echocardiography and electrocardiography. CDT was chosen as the treatment of choice after clinically evaluating risks and benefits in individual patients, comparing them with other therapies such as systemic thrombolysis and after discussing the same with the parents and patients. Each CDT intervention was performed with ultrasound-guided access of femoral vein through which a catheter (5F–7F) was placed in the affected PA. For bilateral PE, catheters were parked in the right and left main PAs, and for unilateral PE, the catheter was parked in the occluded main branch PA. Recombinant tissue plasminogen activator (tPA) was delivered at the thrombus site. UCDT involved ultrasonic pulses delivered by EKOS endowave system along with targeted delivery of tPA. All patients received thrombolytic infusion of tPA (0.75–2 mg/hr per catheter port) with the catheters left in situ for 24 hr. One patient with recurrent PE received a tPA bolus of 10 mg before the start of the infusion. All cases received systemic anticoagulation via heparin infusion. Heparin bolus was administered before the infusion in 4 of the 6 cases. Heparin infusion was administered at 500 U/hr or 10 U/kg/hr during the period of thrombolysis with tPA. After tPA was discontinued, the heparin infusion was titrated to achieve anti-Xa level between 0.3 and 0.7 U/mL and activated partial thromboplastin time between 60 and 90 sec. Coagulation parameters and echocardiographic findings were assessed pre- and post-intervention in all patients. Evolution of PE was evaluated by angiography at 24 hr after intervention.

Definitions and Data Analysis

Complete resolution of PE was defined as no residual thrombus detected by angiography. Partial resolution was defined as resolution of main or major branch PA thrombi but presence of residual clots in peripheral PAs. Treatment-related complications encompassed local or systemic bleeding events and/or need for escalation of cardiorespiratory support. We compared pre- and post-treatment clinical and laboratory parameters for all cases. Clinical parameters were collected as median of values available pre- and post-treatment as median of values over a 24-hr period. The parameters were analyzed with descriptive statistics, paired t test, and Fisher’s exact test as appropriate using STATA software (College Station, TX.).
RESULTS

Patient Demography and Predisposing Factors

Five patients with PE confirmed by computed tomography or conventional angiography underwent 6 CDT interventions during this study period. The median age of patients treated was 16.5 years (range: 11–17). Five of six (83%) interventions were carried out in women. All patients presented with chest pain and dyspnea. All patients had 2 or more predisposing factors for thrombogenesis present at diagnosis. Coexisting lower extremity venous thrombosis and obesity were the most common risk factors and no patients had a malignancy. The demographics and predisposing factors are described in Table I.

Preprocedure Hemodynamics and Laboratory Parameters

Hypotension and need for vasoactive support existed in 2 (33%) cases. Echocardiographic findings were abnormal in all patients. These included depressed RV function with mild-to-moderate tricuspid regurgitation in 4 patients (80%) and 1 patient (20%) had RV strain or hypokinesis before intervention. D dimers were abnormally high in all patients before intervention (median: 9 µg/mL, range: 2–20) and remained high in 4 patients after treatment. All patients needed supplemental oxygen with one being mechanically ventilated before intervention.

Intervention

Three interventions were carried out for extensive bilateral PE, and 3 cases had large occlusive right-sided PA clots. Five of six (83%) interventions were UCDT. All patients had inferior vena cava (IVC) filters placed prior to or concurrent with CDT. Table II describes details of the extent of thrombosis, thrombolytic treatment, evolution of PE, and long-term anticoagulation management of the patients. All patients except 1 (patient 4) who was noncompliant were continued on anticoagulation treatment for at least 6 months. Four interventions were followed by heparin transitioned to enoxaparin as long-term anticoagulation, whereas the other 2 were transitioned directly to enoxaparin. IVC filters were successfully removed at 6–8 months after placement.

### Table I. Demographics and predisposing factors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Predisposing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 years</td>
<td>F</td>
<td>79</td>
<td>LE DVT, obesity, smoking, hypertension, OCP, factor V Leiden mutation</td>
</tr>
<tr>
<td>2</td>
<td>16 years</td>
<td>F</td>
<td>99</td>
<td>Obesity, antiphospholipid syndrome</td>
</tr>
<tr>
<td>3</td>
<td>11 years</td>
<td>M</td>
<td>63</td>
<td>LE DVT, osteomyelitis, staphylococcal bacteremia</td>
</tr>
<tr>
<td>4^</td>
<td>17 years</td>
<td>F</td>
<td>117</td>
<td>Obesity, type 2 diabetes, current LE DVT, elevated factor VIII</td>
</tr>
<tr>
<td>5</td>
<td>17 years</td>
<td>F</td>
<td>47</td>
<td>Klippel–Trenaunay syndrome, current LE DVT</td>
</tr>
</tbody>
</table>

F, female; LE DVT, lower extremity deep vein thrombosis; M, male; OCP, oral contraceptive pills.

^Patient with recurrent PE.

### Table II. Extent of PE and treatment (5 patients with 6 interventions)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Imaging findings</th>
<th>Thrombolysis for 24 hr</th>
<th>Resolution of PE</th>
<th>Post-CDT anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RML, RLL artery occlusive PE</td>
<td>UCDT: tPA 1 mg/hr</td>
<td>Partial Heparin/enoxaparin</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PE extending from main PA to segmental branches</td>
<td>UCDT: tPA 0.75 mg/hr</td>
<td>Complete at 24 hr Enoxaparin/warfarin, aspirin</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Right PA PE with occlusive thrombus RML</td>
<td>UCDT: tPA 1 mg/hr</td>
<td>Partial Enoxaparin/warfarin</td>
<td></td>
</tr>
<tr>
<td>4^</td>
<td>Large Right PA thrombus</td>
<td>UCDT: tPA 1 mg/hr titrated to 2 mg/hr</td>
<td>Complete at 24 hr Heparin/enoxaparin^a</td>
<td></td>
</tr>
<tr>
<td>4’</td>
<td>Bilateral PE</td>
<td>Systemic tPA 10 mg, CDT: 1 mg/hr</td>
<td>Complete at 24 hr Heparin/enoxaparin/warfarin</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Massive bilateral PE</td>
<td>CDT: tPA 1 mg/hr</td>
<td>Complete at 24 hr Heparin/enoxaparin/warfarin</td>
<td></td>
</tr>
</tbody>
</table>

RML, right middle lobe; RLL, right lower lobe.

^aPatient with recurrent PE who was noncompliant at 4 months. 4 and 4’ represent 2 interventions in the same patient.
Outcomes

At 24 hr of CDT therapy, all patients received repeat angiographies. Complete resolution of thrombus was demonstrated after 4 interventions (67%) and partial resolution occurred in 2 instances (Figs. 1 and 2 show imaging findings pre- and post-treatment from 2 patients, one with complete and the other with partial resolution). One patient who had complete resolution of PE at 24 hr after treatment presented with recurrent PE 4 months later and underwent another successful UCDT procedure. Cardiorespiratory parameters improved after each intervention (Table III). Heart rate and respiratory rate decreased, but there was no statistically significant change noted in the oxygenation or blood pressure in our sample. All patients had normalization of RV function on echocardiography postintervention. Median duration of hospital stay was 9 days (range: 7–37). There was no mortality and treatment-related complications occurred.

DISCUSSION

Acute massive or submassive PE featuring or leading to hemodynamic compromise is a serious life-threatening condition requiring prompt intervention. Standard therapy in adults includes anticoagulation with concurrent thrombolytic therapy in patients who have hemodynamic instability. Studies have shown that patients with RV dysfunction have poor outcomes because of the potential for developing RV failure and cardiogenic shock. Emergent systemic thrombolysis facilitates thrombus reduction and improves overall outcomes in this group but is also associated with major bleeding complications. Importantly, even in
patients without absolute contraindications for thrombolysis, there is a reported risk of major hemorrhage of up to 20%. Surgical embolectomy is another treatment option available for patients with massive PE but involves sternotomy, cardiopulmonary bypass, and significant morbidity. CDTs have emerged as an alternative approach that may provide a safe and effective treatment option for severe PE.

The recent scientific statement from the American Heart Association recommends initiation of anticoagulation at initial suspicion of PE and commencement of systemic thrombolysis when RV dysfunction exists. CDT is suggested for patients with massive PE with contraindications to systemic thrombolysis and as a salvage therapy. For submassive PE, CDT is suggested as a consideration for patients with clinical evidence of adverse prognosis but is not recommended for patients with low-risk PE.

CDTs provide the potential advantage of acutely decreasing the thrombus burden with resultant decrease in RV afterload and improvement of hemodynamics. Much smaller doses of thrombolytic agents are used in CDT, leading to fewer complications. Furthermore, adult case series have described various mechanical means used in conjunction with pharmacologic therapies during CDT (pharmacomechanical CDT). Catheter-mediated fragmentation, aspiration, hydrolyzer thrombectomy, rotarex, and rheolytic techniques have been reported to be useful in such settings and hold the potential for reducing bleeding risk compared with systemic thrombolysis.

UCDT has also been used in an effort to dissociate fibrin strands and facilitate dissemination of the thrombolytic agent through the clot. UCDT allows for use of lower doses and shorter infusions of thrombolytics, thereby minimizing adverse effects. The EkoSonic Endovascular Lysus system involves a drug-delivery catheter with multiple lumens and infusion ports. The catheter is placed to have the lumens positioned at the site of the thrombus. Ultrasound energy is generated by an external control unit and is delivered by small transducers uniformly along the infusion system.

Previous pediatric studies evaluating the usefulness of CDT for PE are lacking. Specific information validating safety and efficacy in children and adolescents is critically important, given this age group’s many differences from the typical adult population treated with CDT/UCDT for PE and described in previous reports. In addition to age itself, dissimilar parameters that may lead to differing outcomes between children and adults include body size and weight, ease of vascular access, catheter sizes used, and comorbid conditions. The size of vascular structures in pediatric patients warrants the use of ultrasound in most instances. Furthermore, the concept of developmental hemostasis is well established, whereby plasma concentrations of hemostatic and fibrinolytic factors are known to differ significantly according to age and stage of development. Such differences in underlying physiology and recognized differences in pharmacokinetics and pharmacodynamics of anticoagulants between children and adults highlight the need for specific pediatric studies of CDT/UCDT rather than mere extrapolation from studies in adults.

In our case series, all patients had some form of RV dysfunction, signifying severe (submassive or massive) PE, and were thus felt to be suitable candidates for catheter-based therapies. Five interventions were performed as UCDT, whereas one involved purely CDT. Each intervention resulted in significantly decreased thrombus burden and clinically improved hemodynamic status at 24 hr of treatment. Thereafter, additional thrombolytic infusion was considered to hold greater risk than benefit, and CDT was stopped at 24 hr in each case (Table III). There were no treatment-related adverse events and all patients survived with a relatively short length of hospital stay. Recurrence
of PE occurred in only 1 patient and appeared to be due to noncompliance with the prescribed anticoagulation therapy. Importantly, it was possible to safely reinitiate UCDT in this patient with a successful outcome.

Our case series highlights that CDT and associated thrombus fragmentation techniques used in adults can be used with success in pediatric patients provided the underlying age-related differences in technique to access the vessels, pediatric surgical and perioperative clinical skills, and pharmacology of medications are taken into account. These interventions appear to be safe and efficacious in skilled hands and provide alternatives to systemic thrombolytic therapy. However, our case series is a single-center retrospective study and the sample size limits the ability to gauge the significance of improvement in clinical parameters. In addition, long-term data on RV function and risk of pulmonary hypertension were not available for our patients. However, short-term effects on thrombus resolution and clinical parameters appear promising and prospective evaluation of CDT/UCDT for pediatric PE is warranted.

**CONCLUSIONS**

In our case series of pediatric patients with submassive or massive PE, CDT and UCDT led to partial or complete resolution in each case. These interventional treatment strategies may allow for faster resolution of thrombi with decreased bleeding risk. In the event of recurrence, CDT can be successfully reinitiated. Thus, pediatric patients can be treated with CDT provided that practitioners take into account the variations needed in the treatment from the adult population.

**REFERENCES**


**Table III. Clinical parameters pre- and post-intervention**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (mean ± standard deviation [SD])</td>
<td>110 ± 19</td>
<td>92 ± 21</td>
<td>0.08</td>
</tr>
<tr>
<td>Respiratory rate (mean ± SD)</td>
<td>31 ± 8</td>
<td>20 ± 3.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Oxygen saturation in room air (mean ± SD)</td>
<td>96 ± 1.8</td>
<td>98 ± 1.2</td>
<td>0.105</td>
</tr>
<tr>
<td>Systolic BP (mean ± SD)</td>
<td>104 ± 19</td>
<td>113 ± 13</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic BP (mean ± SD)</td>
<td>59 ± 12</td>
<td>62 ± 15</td>
<td>0.56</td>
</tr>
<tr>
<td>Depressed RV function [Low ejection fraction, n (%)]</td>
<td>4/5 (80)</td>
<td>0/5 (0)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

BP, blood pressure.