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A meta-analysis of outcomes of catheter-directed thrombolysis for high- and intermediate-risk pulmonary embolism

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ABSTRACT

Objective: During the past few years, there has been a surge in the use of catheter-directed thrombolysis (CDT) for acute pulmonary embolism (PE), in the form of either standard CDT or ultrasound-assisted CDT (usCDT). This is a systematic review and meta-analysis of all published series on contemporary CDT for acute PE seeking to determine their clinical efficacy, stratifying by PE severity and CDT modality.

Methods: A comprehensive MEDLINE and Embase search was performed to identify studies that reported outcomes of CDT for acute PE published from 2009 to July 2017. Outcomes included clinical success (in-hospital survival with stabilization of hemodynamics, without decompensation or any major complication), in-hospital mortality, major bleeding, right ventricular/left ventricular ratio, and Miller score changes after CDT. Meta-analyses assumed random effects.

Results: Twenty studies with 1168 patients were included in the meta-analysis. Available for subgroup analysis were 210 patients with high-risk PE and 945 patients with intermediate-risk PE; 181 patients received CDT using a standard multiside hole catheter, and 850 received usCDT. The pooled average right ventricular/left ventricular improvement and Miller score drop after CDT were 0.30 (95% confidence interval [CI], 0.22-0.39) and 8.8 (95% CI, 7.1-10.5). For high-risk PE, the pooled estimate for clinical success was 81.3% (95% CI, 72.5%-89.1%), the 30-day mortality estimate was 8.0% (95% CI, 3.2%-14.0%), and major bleeding was 6.7% (95% CI, 1.0%-15.3%). For intermediate-risk PE, the pooled estimate for clinical success was 97.5% (95% CI, 95.3%-99.1%), the 30-day mortality was 0% (95% CI, 0%-0.5%), and major bleeding was 1.4% (95% CI, 0.3%-2.8%). In high-risk PE, clinical success for CDT and usCDT was 70.8% (95% CI, 53.4%-85.8%) and 83.1% (95% CI, 68.5%-94.5%), respectively. In intermediate-risk PE, clinical success for CDT and usCDT was 95.0% (95% CI, 88.5%-99.2%) and 97.5% (95% CI, 95.0%-99.4%), respectively.

Conclusions: Catheter thrombolysis has high clinical success rates in both high- and intermediate-risk PE, but higher mortality and bleeding rates should be anticipated in high-risk PE. Ultrasound-assisted thrombolysis may be more effective than standard CDT in the higher risk population. (J Vasc Surg: Venous and Lym Dis 2018;6:530-40.)

Keywords: Acute pulmonary embolism; Catheter-directed thrombolysis; Ultrasound-assisted thrombolysis

Acute pulmonary embolism (PE) is a leading cause of in-hospital morbidity and mortality and remains the most common preventable cause of in-hospital death.[1] Its increased incidence during the past two decades, due in part to higher diagnosis rates and an aging population, has driven practice toward newer treatment modalities.[2] The goal of treatment is primarily focused on preventing mortality and secondarily PE recurrence and late-onset respiratory and functional deterioration. Guidelines specify anticoagulation as the standard of care for low-risk PE and escalate therapy to systemic thrombolytics for high-risk (massive) PE associated with hypotension.[3-5] For the intermediate-risk (submassive) PE, defined as cardiopulmonary deterioration (eg, right ventricular [RV] strain, elevated cardiac biomarkers) without hypotension, the risk-benefit ratio may also favor thrombolytic therapy to prevent decompensation.[3-5]

Whereas current evidence is derived from trials using systemic thrombolytics, the high bleeding risk has driven contemporary practice toward catheter-directed thrombolysis (CDT) that is presumed to provide similar therapeutic benefits at a lower complication rate.[6-10] During the past few years, there has been a surge in the use of CDT for PE, in the form of either standard CDT or ultrasound-assisted CDT (usCDT). One randomized trial, registries, and multiple institutional series have been published, yet the numbers are small and the results diverging, so that there is no consensus regarding CDT indications, effectiveness, and safety profile.[10-32] Studies

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are conflicting and have shown that CDT may not be without complications as the reported major bleeding rate ranges widely between 0% and 10%, and failures do exist, although they are not uniformly reported.[7,10,12,27]

The purpose of this systematic review and meta-analysis was to collect contemporary published experience and to provide a higher level of evidence on the clinical efficacy of CDT for acute PE. The meta-analysis is designed to differentiate outcomes between high- and intermediate-risk PE and between CDT using a standard multiside hole catheter and usCDT.

METHODS

Review protocol. The criteria for study selection, methods of analysis, and investigated outcomes were selected before analysis. The protocol was not registered at the International Prospective Register of Systematic Reviews. The review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.[33] No funding was provided for this research.

Study eligibility criteria. Selection of studies was aimed at collecting all studies that included catheter interventions for acute PE. The following eligibility criteria were specified:

1. Studies of 10 or more patients who were treated for acute PE with CDT (standard or usCDT). Standard CDT was defined as any catheter intervention using a standard multiside hole catheter to directly drip lytics into the thrombus, without any other mechanical adjunct. The usCDT was defined as any catheter intervention using the EkoSonic Endovascular System thrombolytic infusion catheters (EKOS Corp, Bothell, Wash).[11]
2. Studies that reported data separated for high- and intermediate-risk PE. High-risk (massive) PE was defined as PE associated with hemodynamic instability, and intermediate-risk (submassive) PE was defined as PE associated with RV strain or elevated cardiac markers in the absence of hemodynamic instability.
3. The sample included adult patients.

Exclusion criteria were the following:

1. Studies that solely involved thrombus fragmentation, rheolytic thrombectomy, rotational thrombectomy, or suction thrombectomy.
2. Studies that did not report any of the primary outcomes.
3. Studies in which an English translation was not available.

Data extraction and outcome measures. Baseline demographics, comorbidities, thrombus scores, echocardiographic parameters, thrombolytic technique (CDT, usCDT), thrombolytic dose, and postinterventional outcomes were extracted. Clinical success was the primary efficacy outcome. Clinical success was a composite outcome defined as decompensation resolution for high-risk PE or prevention of decompensation for intermediate-risk PE in the absence of the following adverse events: major bleeding, stroke, major treatment-related complications (eg, heart or valve injury), need for surgical embolectomy, or in-hospital death. Major bleeding events included intracranial bleeding and any bleeding requiring transfusion or an intervention.

Secondary outcomes included the mean change in RV/left ventricular (RV/LV) ratio and Miller score after CDT.

Search methods. The authors searched the electronic databases MEDLINE and Embase during July 2017. Search dates were limited to the period January 2009 to July 2017 because publications on CDT before 2009 are not relevant to present practice. The search terms used medical subject headings including "catheter," "intervention," "endovascular," "thrombolysis," "thrombectomy," "thromboembolectomy," "lysis," "ultrasound-assisted," "pharmacomechanical," "aspiration," "mechanical," "rheolysis," and "suction" linked by the Boolean operator "OR" and "pulmonary embolism" and "thrombus" likewise linked by "OR." The two groups of terms were then linked across by the Boolean operator "AND." These medical subject heading terms were then converted by a librarian into Emtree vocabulary on Embase. The search was limited to journals published in English and during the date periods mentioned. No contact with authors of manuscripts was necessary.

Two reviewers (Z.S., A.N.A.A.) independently screened the titles and abstracts of all records. The two reviewers extracted the study variables independently. All discrepancies were resolved by consensus led by the senior author (R.A.C.). Reviewers were physicians, with immediate access to senior authors as needed.

Risk of bias assessment. Risk of bias was assessed using a modification of the Newcastle-Ottawa score.[34] Studies were assessed independently by two reviewers (E.D.A., Z.S.) on the basis of selection criteria and ascertainment of outcomes. Selection criteria were determined by the adequacy of case definitions and representativeness of the cases (eg, consecutive case series, definitions of PE risk, and major complications clearly defined). Factors considered in ascertainment of outcomes included uniform clinical and imaging follow-up, clearly defined outcomes, and study design (eg, retrospective chart review vs prospective study with predefined end points).

Statistical analysis. Most of the qualifying studies were retrospective studies with no control group. In anticipation of heterogeneity between studies and as recommended by Borenstein et al,[35] we employed random-effects models, estimating between-study variance with the DerSimonian-Laird method.[36] We assumed a default