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SYSTEMATIC REVIEW: THE ROLE OF THROMBOLYSIS IN INTERMEDIATE-RISK PULMONARY EMBOLISM

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☐ **Abstract—Background: This systemic review provides practicing emergency physicians updated information about the role of thrombolysis in the treatment of intermediate-risk pulmonary embolism. Methods: A PubMed literature search from January 1, 2005 to December 31, 2018 was conducted and limited to human clinical trials written in English with relevant keywords. High-quality studies were identified and then underwent a structured review. Recommendations are made based on the literature review. Results: Sixty-three articles met criteria for rigorous review, of which 13 were appropriate for citation in this review. Of these 13, there were 6 prospective studies and 7 retrospective studies. Conclusions: Thrombolysis, either catheter-directed or systemic, is a treatment option in the management of patients with intermediate-risk pulmonary embolism and a high likelihood of clinical deterioration. Each method of thrombolysis carries risks and benefits. Based on the available evidence, transfer to a facility for the purpose of catheter-directed thrombolysis is not recommended.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—pulmonary embolism; submassive; intermediate risk; thrombolytics**

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INTRODUCTION

Pulmonary embolism (PE) remains a leading cause of cardiovascular mortality, resulting in an estimated 150,000 deaths annually in the United States (1,2). With a 3-month mortality rate of 9–15%, PE presents an important clinical problem (3,4). Until recently, there has been little change in the treatment options for PE, with guideline recommendations of anticoagulation only in all but the most critically ill presentations (5,6). Newer catheter-directed therapies, most notably catheter-directed thrombolysis (CDT), present another treatment option purported to improve safety and efficacy.

PE is typically categorized as high risk (massive), intermediate risk (submassive), or low risk. High-risk PE carries the highest probability of mortality and is defined by persistent hypotension (systolic blood pressure < 90 mm Hg) or cardiovascular collapse (2,7). High-risk PE has a universal recommendation from the American Heart Association and American College of Chest Physicians for full-dose systemic thrombolytics, provided there are no absolute contraindications (5,8). Patients with PE who are normotensive without evidence of right ventricle (RV) strain on echocardiography or computed tomography (CT) scan or elevated serum biomarkers (troponin/B-type natriuretic peptide) are considered to

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have low-risk PE, which carries a roughly 1% mortality rate (9,10). Patients with PE and evidence for associated RV strain, or elevation of serum biomarkers but without hypotension are categorized as having intermediate-risk PE.

Intermediate-risk PE accounts for 20–40% of presentations and is the source of the current treatment controversy (4,11). Variable criteria for the diagnosis of intermediate-risk PE and conflicting evidence for the use of thrombolysis has led to confusion (5). PE with RV dysfunction or elevation of serum biomarkers has been linked to increased mortality (12–14). Long-term exercise intolerance secondary to chronic thromboembolic pulmonary hypertension (CTEPH) has also been associated with RV dysfunction seen at the time of PE diagnosis (15–19).

Increased mortality and the fear of long-term morbidity associated with intermediate-risk PE have led to the pursuit of more aggressive therapeutic options. Thrombolysis, both systemic and catheter-directed, has been promoted in the treatment of intermediate-risk PE. Unfortunately, there is no consensus on the optimal medication delivery, either systemic or via a catheter placed directly into the pulmonary vasculature. Controversy remains about which patients would benefit from interventions that carry a potential increased risk of bleeding, stroke, and death.

This article reviews the current medical literature for using thrombolysis in patients with intermediate-risk PE and offers evidenced-based recommendations to emergency physicians. This work was done at the request of, and published as a clinical practice statement by, the American Academy of Emergency Medicine Clinical Guidelines Committee.

MATERIALS AND METHODS

A structured review of the medical literature using PubMed was performed and limited to studies published between January 1, 2005 and December 31, 2018. Inclusion criteria were all clinical trials involving human subjects, written in the English language, and containing the following keywords: *pulmonary embolism* AND (*thrombolysis* OR *thrombolytics* OR *catheter-directed*) AND *intermediate*; or *pulmonary embolism* AND (*thrombolysis* OR *thrombolytics* OR *catheter-directed*) AND *submassive*. References of the selected articles were also screened to search for potential additional relevant studies. The abstracts of the articles found in this search were assessed independently by two of the authors to determine which papers were relevant for a more detailed review. Studies included for the final detailed review were limited to randomized controlled trials, prospective cohort trials, and retrospective case–control or case–cohort studies. Case series, case reports, and opinion pieces were excluded. General review articles and abstracts presented at conferences were not included for formal review.

Each of the selected articles was subjected to detailed review by at least two of the authors. The level of the evidence was assigned a Grade of Evidence using the definitions as noted in Table 1 and were based on reference focus, specific research design, and methodology. Each of the selected articles was also subjected to detailed review and assigned a quality ranking based on a critical assessment with regard to quality of the design and methodology. This includes design consideration (ie, focus, model structure, and presence of controls) and methodology consideration (actual methodology utilized). The definitions of the quality ranking scores are included in Table 2. Independent review of the articles as well as discussion and joint review by the authors were undertaken to answer the clinical questions.

Finally, recommendations were made based on the review of the literature and assigned a level of recommendation, as defined in Table 3.

RESULTS

The search parameters for the term *pulmonary embolism/thrombolytics pulmonary embolism/thrombolysis* resulted in 306 unique articles of human studies. Two emergency physicians independently assessed the abstracts of the articles. A total of 63 articles were deemed appropriate to be pulled for additional screening. From these 63 articles, 13 met criteria for rigorous review and citation in this article (6 prospective studies and 7 retrospective studies). Table 4 lists the selected references with their appropriate grade and quality of evidence classification.

Table 1. Definitions of the Criteria Used in Assigning a Grade of Evidence Review to the Articles

Grade	Description
A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue
B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
C	Prospective, controlled, non-randomized, cohort studies
D	Retrospective, non-randomized, cohort or case-control studies
E	Case series, animal/model scientific investigations, theoretical analyses, or case reports
F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

Table 2. Definitions Used to Assign a Quality Ranking Scores for the Included Articles

Ranking	Design Consideration Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with possible bias	Adequate	No, either present
Poor	Limited or biased	Limited	No, either present
Unsatisfactory	Questionable/none	Questionable/none	No, either present

The primary goal of this literature search was to determine the evidence for using thrombolysis in patients with intermediate-risk PE.

Question 1: Should Thrombolytics Be Administered to Patients with Intermediate-Risk PE?

The current literature is clear that thrombolysis in intermediate-risk PE effectively reduces RV dilation and right heart pressures compared to anticoagulation alone; however, the clinical relevance of this is uncertain (21,26,29,33). Short-term results for these variables have been dramatic, but their utility is questionable without demonstrating significant improvement in patient-centered outcomes (eg, mortality, long-term physical symptoms, and reduction of CTEPH risk). The largest randomized trial, conducted by Meyer et al., showed a decrease in hemodynamic decompensation at 7 days, but no difference in RV dysfunction, CTEPH, or mortality at 2 years (28,31).

Other studies support the use of thrombolysis in PE, however, almost all contain major flaws, including small size, non-randomized design, or failure to measure meaningful patient-centered outcomes. The heterogeneity of these articles makes a meta-analysis much less valuable, though several have been attempted (22–25,27,30). The inability to detect differences in important clinical outcomes, such as mortality, may be due to the characterization of low-risk patients as intermediate risk. Several studies have shown a 0–3% mortality for their intermediate-risk group, which is similar to that described previously in low-risk PE (1%), making a difference difficult to detect (23,24,29,32). Distinguishing intermediate-risk PE patients at the highest risk for decompensation or death is necessary before a therapeutic benefit, if one exists, can be identified.

Conclusion. Systemic thrombolysis is a treatment option in the management of patients with intermediate-risk PE and a high likelihood of clinical deterioration.

Level of evidence: class indeterminate.

Question 2: Should Catheter-Directed Thrombolytics Be Administered to Patients with Intermediate-Risk PE?

The ability to administer thrombolytics directly into the pulmonary circulation or even the thrombus itself with a centrally placed catheter has led investigators to assume lower dosing can be utilized, while maintaining the same efficacy (20,26). Guidelines generally suggest systemic thrombolytic therapy using a peripheral vein over CDT; however, it is suggested CDT be considered for patients with high bleeding risk, failed systemic thrombolysis, or shock that is likely to cause death before systemic

Table 3. Definitions Used for Determining Recommendations

Level of Recommendation	Criteria for Level of Recommendation	Mandatory Evidence
Class A (recommended with outstanding evidence)	Acceptable Safe Useful Established/definitive	Level A/B grade Outstanding quality Robust All positive
Class B (acceptable and appropriate with good evidence)	Acceptable Safe Useful Not yet definitive	Level A/B grade lacking Adequate to good quality Most evidence positive No evidence of harm
Class B1	Standard approach	Higher grades of evidence Consistently positive
Class B2	Optional or alternative approach	Lower grades of evidence Generally, but not consistently, positive
Class C (not acceptable or not appropriate)	Unacceptable Unsafe Not useful	No positive evidence Evidence of harm
Class Indeterminate (unknown)	Minimal to no evidence	Minimal to no evidence

Table 4. Summary of 13 Articles Reviewed in Depth

No.	First Author	Grade	Quality	Design	Finding
1	Avgerinos (20)	D	Outstanding	Case–control study of 64 IRPE patients who received CDI compared to 64 controls who received AC alone.	No difference in mortality, major bleeding, or long-term dyspnea. CDI patients had faster restoration of RV function, but had higher complication rates.
2	Bagla (21)	D	Good	Retrospective cohort study of 45 IRPE patients who received CDI.	mPAP decreased significantly, as did RV dilation.
3	Bajaj (22)	D	Outstanding	Single-arm meta-analysis (no control group) of observational data.	After CDT, mPAP and RV dilation improved; major bleeding rates varied between studies.
4	Bloomer (23)	D	Outstanding	Retrospective cohort study of 137 PE patients treated with CDI (88% IRPE).	After CDT, mPAP and RV dilation improved. ICH in 2 patients, major complications in 9.4%.
5	Chatterjee (24)	B	Outstanding	Meta-analysis of RCTs. Included 1775 patients with IRPE.	In IRPE, thrombolysis was associated with lower mortality (OR 0.48; 95% CI 0.25–0.92) and more bleeding events (OR 3.19; 95% CI 2.07–4.92).
6	Hao (25)	B	Outstanding	Cochrane review of RCTs comparing thrombolytic therapy to anticoagulation for PE.	Low-quality evidence that thrombolytics reduce death following acute PE compared to heparin.
7	Kaymaz (26)	D	Good	Retrospective cohort of 75 (60 IRPE) patients who underwent CDT.	In IRPE, CDT thrombolysis was associated with decreased mPAP and mean RV dilation.
8	Kaymaz (27)	A	Outstanding	Meta-analysis of PE patients receiving thrombolysis.	In IRPE, CDT thrombolysis was associated with decreased mPAP and mean RV dilation.
9	Konstantinides (28)	A	Outstanding	Long-term (> 2 years) follow-up of patients in the Meyer study.	No difference in mortality, persistent dyspnea, or RV dysfunction.
10	Kuchar (29)	A	Outstanding	RCT of 59 IRPE patients comparing CDI vs. AC alone.	CDI group had significantly better improvement in RV dilation.
11	Lou (30)	D	Good	Meta-analysis of 422 IRPE patients (of primarily retrospective cohort studies) who received CDI.	In IRPE, CDT thrombolysis was associated with decreased mPAP and mean RV dilation.
12	Meyer (31)	A	Outstanding	RCT of 1006 IRPE patients comparing systemic thrombolysis with placebo.	No difference in short-term mortality. Active treatment patients had less hemodynamic decompensation but more major hemorrhage and stroke.
13	Nakamura (32)	A	Adequate	Meta-analysis of RCTs comparing thrombolysis for IRPE vs. AC alone.	No difference in mortality or recurrent PE but clinical deterioration was decreased.

AC = anticoagulation; CDI = catheter-directed intervention; CDT = catheter-directed thrombolysis; CI = confidence interval; ICH = intracerebral hemorrhage; IRPE = intermediate-risk pulmonary embolism; mPAP = mean pulmonary artery pressure; OR = odds ratio; PE = pulmonary embolism; RV = right ventricular.

thrombolysis can take effect (5). Lower-dose thrombolytics (≤25% of full stroke dose) in combination with reduced heparin dosing is believed to dramatically reduce the risk of bleeding, however, it is unclear if similar results could be achieved using the same treatment administered peripherally (34).

The direct comparison of CDT to peripheral thrombolysis for intermediate-risk PE in particular does not exist, other than a small study from 30 years ago, which found no difference between these treatment modalities (35). Doses roughly 25% of full-dose thrombolysis are common among CDT trials, while in the trial by Meyer et al., full-dose thrombolysis was used with an aggressive heparin regimen (28,31). This more aggressive dosing may have led to the high rates of major extracranial bleeding (6.3%) and hemorrhagic stroke (2%) not seen in the lower-dose CDT trials (< 1%) (33). More frequently occurring serious complications of therapy could have masked any potential benefit. Reduced dosing of peripheral thrombolytics may provide the same efficacy with a comparable safety profile. Peripheral thrombolytics could be administered without the need for central catheter placement or interventional specialists that may not be available without transfer. Clinical trials comparing CDT with systemic thrombolysis are needed before a judgment of superiority can be made.

Conclusion. Catheter-directed thrombolysis is a treatment option in the management of selected patients with intermediate-risk PE and a high likelihood of clinical deterioration. Based on the available evidence, transfer to a facility for the purpose of catheter-directed thrombolysis is not recommended.

Level of evidence: class indeterminate.

DISCUSSION

This review of the available medical literature focused on the treatment of intermediate-risk acute PE with thrombolysis. The literature addressing this topic is limited by small sample sizes, the use of surrogate outcomes, and heterogeneous methods. Further randomized studies will be needed to clarify the population that will benefit from thrombolysis. The available randomized data suggest that systemic thrombolysis administered to intermediate-risk PE patients may decrease the risk of hemodynamic compromise acutely, but does not affect mortality. It also does not decrease the rate of chronic respiratory symptoms or pulmonary hypertension in the long-term, but does increase bleeding risk. Thus, it should be reserved for patients at risk of hemodynamic collapse.

The literature for CDT is weak. At a center where CDT is available, it can be considered in the appropriate patient. However, due to the paucity of evidence for its use, transferring a patient for this procedure is not recommended.

Limitations

The review of the clinical question addressed in this article is limited by the quantity and quality of publications on this topic. Also, the structure and search parameters of this literature review may have resulted in information being omitted.

CONCLUSIONS

Convincing evidence regarding the benefit of CDT for patients with intermediate-risk PE does not exist. The transfer of a patient for the purpose of CDT due to lack of local availability is not currently recommended. In a patient with massive PE who also has substantial bleeding risk or relative contraindications to thrombolytics, CDT is reasonable (if available) in order to allow the lowest possible dosing. Thrombolysis may eventually prove advantageous when a population with the highest chance for decompensation, yet not massive PE, is identified. This group may be more likely to benefit from a therapy with potential hazards. CDT may have greater efficacy or enable lower thrombolytic dosing; however, this has not yet been proven. Utilization of thrombolysis for intermediate-risk PE should be used only with a shared decision-making approach explaining the risks and benefits of therapy. This shared decision should be reserved for those who carry the greatest likelihood of deterioration.

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