Clinical Practice Statement

What is the Role of Thrombolysis in Intermediate Risk Pulmonary Embolism?

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Recommendation

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 upon the available evidence, transfer to a facility for the purpose of catheter-directed thrombolysis is not recommended.

Introduction

Pulmonary embolism (PE) remains a leading cause of cardiovascular mortality[1] resulting in an estimated 150,000 deaths annually[2] in the United States. With a 3-month mortality rate of 9-15%,[3,4] PE presents an important clinical problem. 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. Published evidence in the currently available literature is weak and the conclusions do not seem to be justified.

Executive Summary

PE is 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 mmHg) 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.[8,9] Patients with PE who are normotensive without evidence of right ventricle (RV) strain on echocardiography or computed tomography (CT)[10] scan or elevated serum biomarkers (troponin/BNP) are considered to have low risk PE which carries a roughly 1% mortality.[11] Patients with PE associated evidence of RV strain and/or elevation of serum biomarkers but without hypotension are categorized as having intermediate risk PE.

Intermediate risk PE accounts for 20% to 40% of presentations and is the source of current treatment controversy.[4,12] 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[12,13] or elevation of serum biomarkers[14-16] has been linked to increased mortality. 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.[17-21] Increased mortality and the fear of long term morbidity associated with intermediate risk pulmonary embolism has 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 regarding which patients would benefit from interventions that carry a potential increased risk of bleeding, stroke and death.

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.[22-25] Short-term results for these variables have been dramatic, but their utility is questionable without demonstrating significant improvement in patient-centered outcomes (i.e., mortality, long term physical symptoms, reduction of CTEPH risk, etc.). The largest randomized trial, conducted by Meyer et al, showed no difference in RV dysfunction, CTEPH or mortality at three years.[26] Several articles support the use of thrombolysis in PE, however, almost all contain major flaws including small size, non-randomized design, or they fail to measure meaningful patient-centered outcomes. The heterogeneity of these articles makes a meta-analysis much less valuable, though several have been attempted.[27-32] 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% to 3% mortality for their intermediate risk group, which is similar to that previously described in low risk PE (1%) making a difference difficult to detect.[22,27,28,33] 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.

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.[24,34] Lower dose thrombolytics (25% or less of full stroke dose) in combination with reduced heparin dosing is felt to dramatically reduce the risk of bleeding[35], however, it is unclear if similar results could be achieved using the same treatment administered peripherally. 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.[36] Doses roughly 25% of full dose thrombolysis are common among CDT trials, while in the trial by Meyer et al,[26] full dose thrombolysis was used with an aggressive heparin regimen. 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%).[23] 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 judgement of superiority can be made.

Conclusion

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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