Should patients with submassive pulmonary embolism be thrombolysed?

Thrombolysis can be used to break down a pulmonary embolism more rapidly than standard anticoagulation. Its use has been confined to patients with massive pulmonary embolism and haemodynamic collapse, with disagreement over its role in submassive pulmonary embolism because of the risk of catastrophic bleeding.

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Introduction

Pulmonary embolism can have a huge range of clinical presentations, from fatal to asymptomatic, so risk stratification is key to guide treatment. High-risk, or massive pulmonary embolism is characterised by haemodynamic instability (systolic blood pressure of less than 90 mmHg or cardiac arrest) and occurs in 5% of cases. In these circumstances, thrombolysis with fibrinolytic agents can be considered as initial treatment (Duffett et al, 2020). Intermediate-risk, or submassive pulmonary embolism is defined by normotension but with features of right heart strain or myocardial injury. These can be diagnosed by echocardiography or elevated troponin levels respectively, and are seen in as many as 25% of patients with acute pulmonary embolism (Konstantinides et al, 2019). These patients are at increased risk of haemodynamic deterioration and early death, as well as developing chronic thromboembolic pulmonary hypertension (Duffett et al, 2020). For this reason controversy remains as to whether these patients should receive the more potent, yet potentially dangerous, fibrinolytic therapy or standard anticoagulation. Low-risk pulmonary embolism fulfils neither criteria, is treated with standard anticoagulation and is the only category that should be considered for outpatient management (Konstantinides et al, 2019; National Institute for Health and Care Excellence, 2020).

Benefit of thrombolysis

The PETHIO trial remains the largest, well-designed study of patients with intermediate-risk pulmonary embolism. It demonstrated a reduction in mortality in the first 7 days from 5.6% in the anticoagulation group to 2.6% in the thrombolysis group (Becattini et al, 2014), but at 30 days there was no significant difference in survival between the two treatment groups. The authors noted that this was likely because a number of the control group went on to receive rescue thrombolysis for haemodynamic deterioration after randomisation, thus improving the survival of the anticoagulation group (Becattini et al, 2014). Meta-analysis of a further seventeen studies supports the finding that thrombolysis in patients with pulmonary embolism at any level of risk reduces all-cause mortality (Duffett et al, 2020).

Risk of thrombolysis

The biggest risk associated with systemic thrombolysis is major bleeding, which has been reported at higher than 10% (Duffett et al, 2020). Haemorrhagic stroke is the most devastating consequence of bleeding, leading to death or significant disability. Those undergoing fibrinolytic therapy for pulmonary embolism have a 10-fold increased risk of an intracranial bleed (Becattini et al, 2014). In addition, thrombolysis in patients with submassive pulmonary embolism may not have the long-term benefits that have been suggested. Three-year follow up from the PETHIO study showed that, despite early clot disruption and initial mortality benefit, there was no decrease in the long-term rates of right heart dysfunction or mortality in patients who received thrombolysis (Duffett et al, 2020).

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Integrated strategies

Although evidence suggests that certain patients with submassive pulmonary embolism may benefit from thrombolysis, the risk of major bleeding is high. The American College of Chest Physicians do not recommend thrombolysis for patients without hypotension (Kearon et al, 2016), but advise treatment with systemic anticoagulation and close monitoring to facilitate quick thrombolysis if signs of deterioration are detected. These include hypotension, increasing right heart strain, worsening gas exchange and increasing jugular venous pressure (Kearon et al, 2016). The European Society of Cardiology guidelines also recommend initial treatment with conventional anticoagulation but with the option for systemic thrombolysis in the case of haemodynamic deterioration (Konstantinides et al, 2019). There is currently no guidance available from the British Thoracic Society.

Alternatives to full-dose systemic thrombolysis

Alternatives to traditional thrombolysis aim to reduce the risk of bleeding and include percutaneous, catheter-directed therapy and low-dose thrombolytic regimens. Studies suggest that catheter-directed therapy improves right ventricular function without an increased risk of bleeding, but the evidence is weak because the study sizes are small (Kearon et al, 2016; Konstantinides et al, 2019). Use of catheter-directed therapy is limited by its availability. Meta-analysis of low-dose systemic thrombolysis suggested that it is associated with the lowest overall probability of dying compared to other treatments, although these results were not statistically significant in terms of mortality benefit or bleeding risk because of a paucity of evidence (Jimenez et al, 2018). These treatments require further investigation before widespread implementation.

Conclusions

Given the current evidence, the author believes that thrombolysis should only be considered as initial therapy for patients with high-risk pulmonary embolism. Those with intermediate-risk pulmonary embolism should not be thrombolysed immediately but instead admitted to a high dependency unit where they can have continuous blood pressure monitoring for early detection of haemodynamic instability. The far-reaching consequences of intracranial bleeding make shared decision making even more important. Patients admitted with submassive pulmonary embolism should have a frank pre-emptive discussion with clinicians regarding thrombolysis to allow fully informed consent before any deterioration.

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