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Thrombolytic therapy for pulmonary embolism: lessons from recent clinical trials

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Abstract

Pulmonary embolism is a common disease that is associated with significant mobility and mortality. Thrombolysis is potentially life saving when used in conjunction with anticoagulant therapy. Indications for thrombolysis for pulmonary embolism are not well defined. In patients with acute massive pulmonary embolism and hypotension, thrombolytic therapy offers some benefits in terms of mortality reduction. The use of thrombolysis in patients with stable haemodynamics has been controversial for more than two decades. Recent clinical studies have indicated that thrombolytic treatment in conjunction with heparin in patients with submassive pulmonary embolism and normal blood pressure can prevent deterioration of the disease and diminish the need for more intensive therapies during hospitalisation. The role of prehospital thrombolytic therapy for acute pulmonary embolism is unclear and further clinical studies are warranted.

Keywords

emergency medical services; emergency medical technicians; heparin; prehospital; pre-hospital; pulmonary embolism; thrombolysis; thrombolytic therapy.

Introduction

Pulmonary embolism is a medical emergency and a major cause of morbidity and mortality, affecting 0.5-1.0 per 1,000 people in the general population each year.[1,2] It often leads to pulmonary hypertension and right-sided heart failure. Patients with right ventricular dysfunction due to pulmonary embolism have increased rates of in-hospital death, even in the absence of arterial hypotension or shock.[1-3] In-hospital mortality rate can be as high as 30% in those with unstable haemodynamics at presentation.[2,3]

Anticoagulation with heparin and warfarin remains the mainstay of treatment for pulmonary embolism.[2,3] The primary objectives of anticoagulant therapy are to diminish the propagation of the existing thrombus and to prevent recurrence. Thrombolysis has also been used to treat acute massive pulmonary embolism accompanied by haemodynamic instability or cardiogenic shock.[4] However, the use of thrombolysis in patients with submassive pulmonary embolism and normal blood pressure has been controversial.

Anticoagulant therapy for pulmonary embolism

The therapeutic goals for acute pulmonary embolism are to relieve symptoms, prevent the development of pulmonary hypertension and right ventricular failure, and ultimately, diminish the risk of death. Long-term prevention of recurrence should also be considered in all patients. To achieve these therapeutic objectives, anticoagulation has been widely used, where unfractionated heparin or low-molecular- weight heparin is to be used for about a week, followed by oral administration of warfarin for at least 3-6 months.[3] Heparin provides immediate anticoagulation and severs as a bridge until warfarin is fully effective.

Either unfractionated heparin or low-molecular-weight heparin can be used as the initial anticoagulant therapy to reduce the size of the thrombus and prevent recurrence of pulmonary embolism.[3] Both types of heparin have similar efficacy.[5] However, low-molecular-weight heparin has the advantage that, when subcutaneously injected on a body-weight-based dose regimen, it achieves an immediate anticoagulation effect without frequent dose adjustment or monitoring of activated partial thromboplastin time.[5]

The potential adverse effects of heparin are haemorrhage and thrombocytopenia.[5, 6] The risk of major bleeding is 1.0-5.0%, which increases with age (>70 years) and the dose of heparin.[6] Low molecular weight heparin is associated with less major bleeding, such as intracranial or retroperitoneal haemorrhage, compared with unfractionated heparin in acute venous thromboembolism.[6]

Warfarin is effective in reducing the risk of recurrent pulmonary embolism by up to 90%, if the target international normalised ration (INR) is maintained between 2.0-3.0.[7] Higher intensity warfarin treatment with a target INR between 3.1-4.0 does not appear to be more effective than the standard intensity warfarn in preventing the recurrence of pulmonary embolism.[8]

Warfarin is associated with major bleeding in 0.5-2.5 per 100 patients per year.[9] Patients with similar INR during warfarin therapy may experience significant variability in coagulation responses and widely different risk of bleeding.[9]

Thrombolysis for pulmonary embolism

Thrombolytic drugs such as urokinase, streptokinase or recombinant tissue plasminogen activator (tPA) act by converting plasminogen to plasmin, which dissolves the thrombus. The main reason for thrombolytic therapy is that, in conjunction with anticoagulation, it may reduce the risk of pulmonary hypertension, right ventricular dysfunction or rate of death.[10]

The evaluation of thrombolytic therapy for pulmonary embolism began in the early 1970s. The first prospective randomised trial was the Urokinase Pulmonary Embolism Trial (UPET), where the effect of urokinase and heparin was compared in patients with acute pulmonary embolism.[11] Within 24 hours of the drug administration, improvement in lung scans, pulmonary angiograms and right ventricular pressure was found only in the urokinase group.[11] However, no significant differences in clinical outcomes were apparent between the two groups 24 hours after the drug administration.[11]

The effect of urokinase was also compared with streptokinase in a second phase study of UPET.[12] The effects on lung scans were similar between the two agents; both were superior to heparin only treatment within 24 hours of the drug administration.[12]

The effect of tPA on pulmonary embolism was initially investigated in a small group of patients. Compared with heparin only therapy, a tPA, alteplase, led to a greater reduction in pulmonary pressure and better improvement in pulmonary angiography.[13] However, even there were significant improvements in the objective tests, no additional clinical benefits were observed in the thrombolytic therapy group.[13]

Further studies were conducted by Goldhaber and associates [14] and the European Cooperative Study investigators [15] to compare the effect of tPA and urokinase. These studies demonstrated that, although tPA initially produced a faster resolution of the pulmonary thrombus, clinical outcomes were the same 24 hours after the drug administration.

The impact of thrombolysis on mortality in patients with pulmonary embolism has been a subject of debate for many years. A recent meta-analysis on some major clinical trials on thrombolytic therapy has found that, compared with heparin, thrombolytic therapy is not associated with a statistically significant reduction in recurrent pulmonary embolism or death.[16] However, in trials that enrolled patients with massive pulmonary embolism and hypotension or cardiogenic shock, thrombolytic therapy is associated with a significant reduction in recurrent pulmonary embolism or death.[16]

Thrombolysis in patients with pulmonary embolism is associated with a significant risk of major bleeding. The bleeding rates from thrombolysis are higher than that from heparin. Pooled data from recent trials on pulmonary embolism have demonstrated that, major bleeding rate in thrombolysis and heparin group is 9.1% and 6.1%, respectively.[16] The rate of nonmajor bleeding in the thrombolysis group was also higher than that in the heparin group (22.7% vs 10.0%).[16]

Due to the perceived lack of mortality benefit and long-term efficacy, thrombolysis has been mainly used for the management of massive pulmonary embolism, which is often accompanied by hypotension or cardiogenic shock.[17] The role of thrombolytic therapy in patients with submassive pulmonary embolism and stable haemodynamics remains uncertain. A recent trial, the Management Strategies and Determinants of Outcome in Acute Pulmonary Embolism Trial 3, one of the largest trials in the field involving 256 patients, shows that, compared with heparin only treatment, alteplase (100 mg over 2 hours) plus heparin substantially reduces the need for intensive therapeutic measures such as mechanical ventilation, pressor agents or secondary thrombolysis during hospitalisation.[18] However, a reduction in death has not been demonstrated in the heparin-plus-alteplase group.[18]

Prehospital thrombolysis for pulmonary embolism

Little is known about the role of prehospital thrombolytic therapy for acute pulmonary embolism. There have been some isolated case reports where prehospital administration of thrombolytics enhances the survival of patients presented with cardiac arrest following massive pulmonary embolism.[19] A multi-centre clinical trial is currently underway to assess if prehospital thromblitic therapy would improve the short-term survival rates in cardiac arrest patients following acute pulmonary embolism or myocardial infarction.[20] Empirical administration of thrombolytic agents in the prehospital setting may be a reasonable course of action today when patients with known deep venous thrombosis suddenly become short of breath and hypotensive, suggesting the occurrence of pulmonary embolism.

Because most patients with pulmonary embolism require diagnostic tests in hospitals and there is no simple and reliable method to make a clinical diagnosis outside of the hospitals,

treating this condition during prehospital setting remains difficult. Perhaps the most important prehospital management is to transport the patient to a hospital as quickly as possible.

Conclusions

Thrombolysis together with unfractionated or low-molecular-weight heparin appears to be an effective therapeutic strategy for patients with massive pulmonary embolism and unstable haemodynamics. This treatment improves clinical symptoms and reduces pulmonary pressure, diminishing the risk of right ventricular failure or death. However, the role of thrombolysis in patients with pulmonary embolism but stable haemodynamics remains uncertain. Further studies are required to clarify the role of prehospital thrombolytic therapy for acute pulmonary embolism.

References

1. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998; 158: 585-93.
2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386-9.
3. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997; 30:1165-71.
4. Dalen JE, Alpert JS, Hirsch J. Thrombolytic therapy for pulmonary embolism: is it effective? Is it safe? When is it indicated? Arch Intern Med 1997; 157:2550-6.
5. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for the treatment of pulmonary embolism: a meta-analysis of randomized controlled trials. Ann Intern Med 2004; 140; 175-83.
6. Levine MN, Raskob G, Beyth RJ, et al. Hemorrhagic complications of anticoagulant treatment. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126: 287S-310S.
7. Goldhaber S, Elliot C. Acute pulmonary embolism: part II: risk stratification, treatment, and prevention. Circulation 2003; 108: 2834-8.
8. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome. N Engl J Med 2003; 349: 1133-8.
9. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126 (3 Suppl): 401S-28S.
10. Konstantinides S, Geibel A, et al. Association between thrombolytic treatment and the prognosis of haemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation 1997; 96:882-8.
11. Urokinase pulmonary embolism trial: Phase I results. A cooperative study. JAMA 1970; 214:2163-72.
12. Urokinase-streptokinase embolism trial: Phase 2 results. A cooperative study. JAMA 1974; 229:1606-13.
13. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. J Am Coll Cardiol 1992; 20:520-6.
14. Goldhaber SZ, Kessler CM, Heit J, et al. Randomised controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. Lancet 1988; 2:293-8.
15. Meyer G, Sors H, Charbonnier B, et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism. The European Cooperative Study Group for Pulmonary Embolism. J Am Coll Cardiol 1992; 19:239-45.
16. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for initial treatment of pulmonary embolism: a meta-analysis of randomized controlled trials. Circulation 2004; 110: 744-49.
17. Goldhaber SZ. Pulmonary embolism. Lancet 2004; 363:1295-305.
18. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, for the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002; 347:1143-50.

19. Kuisma M, Silfvast T, VoipioV, Malmstrom R. Prehospital thrombolytic treatment of massive pulmonary embolism with reteplase during cardiopulmonary resuscitation. Resuscitation 1998; 38: 47-50.
20. Spohr F, Arntz HR, Bluhmki E, et al. International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. Eur J Clin Invest 2005; 35:315-23.

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