Update on Thrombolytic Therapy in Acute Pulmonary Thromboembolism

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ABSTRACT

Thrombolytic treatment accelerates the dissolution of thrombus in acute pulmonary thromboembolism (PTE) and is potentially a lifesaving treatment. High-risk PTE is the clearest indication for this therapy, and its use in intermediate-risk cases is still controversial. A PTE response team may enable a rapid and effective determination of risk and treatment in these controversial clinical cases. Approved thrombolytic agents for the PTE treatment are streptokinase, urokinase, and alteplase. Currently, the most widely used agent is alteplase. It has a short infusion time (2 h) and a rapid effect. Newer, unapproved agents for the PTE treatment are tenecteplase and reteplase. The active resolution of thrombus via thrombolytic agents improves rapidly pulmonary perfusion, hemodynamic defect, gas exchange, and right ventricular dysfunction. However, it is important to determine appropriate candidates carefully, to prevent hemorrhage, which is the most important side effect of these drugs. Catheter-directed thrombolysis seems to be an alternative in patients not eligible for systemic thrombolytic therapy.

Keywords: Pulmonary embolism, thrombolytic therapy, fibrinolytic agents

Introduction

Pulmonary thromboembolism (PTE) is a common disease that may be life threatening. The mortality rate can reach up to 65% in high-risk patients [1]. Most deaths occur within the first hour of patients presenting with shock; therefore, the survival of these patients depends on rapid treatment [2-4].

PTE is usually the result of pulmonary artery obstruction by a thrombus formed in the deep veins of the legs or the pelvic veins. Comorbidities (e.g., chronic obstructive pulmonary disease [COPD], congestive heart disease, cerebrovascular diseases); recent surgery (particularly pelvic or lower abdominal surgeries); pregnancy, active cancer, chemotherapy, oral contraceptive, or hormone replacement therapy; and genetic risk factors (e.g., prothrombin G20210A, Factor V Leiden mutation) increase the PTE risk [5, 6]. In addition, seasonal pressure changes may also induce the development of embolism [7]. Hypoxia caused by both seasonal pressure changes and COPD can trigger thrombus formation. The studies have shown that COPD both increases the risk of embolism and the risk of mortality in patients with embolism [8-10].

Risk assessment in patients diagnosed with PTE is important to initiate effective treatment as early as possible and prevent mortality. The currently recommended approach is to establish a pulmonary embolism response team (PERT) [10, 11]. This enables rapid and effective determination of risk and treatment, especially in controversial clinical cases. Evaluating early (30 days) clinical risk in PTE patients requires physical examination, echocardiographic (ECHO) imaging of the heart or in thoracic computed tomography angiography (CTA) RV/LV (right ventricle/left ventricle) ratio, and cardiac biomarkers (N-terminal brain natriuretic peptide [NT-BNP] and troponin). The presence of RV dilation or RV free wall hypokinesis in ECHO is associated with an increased mortality risk, even if the patient is stable [12, 13]. Of the current guidelines, the European Society of Cardiology recommends using the pulmonary embolism severity index (PESI) or simplified PESI (sPESI) for clinical risk assessment of patients with PTE. Patients are categorized as intermediate- or low-risk, based on whether sPESI score is >1, and according to the presence of RV dysfunction (ECHO or computed tomography) and positivity of cardiac biomarkers. However, if PTE patients show

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signs of hypotension or shock at presentation, they are considered high-risk regardless of these parameters [3]. The guidelines of the American Heart Association do not use PESI or sPESI for risk assessment. Patients are classified as massive, submassive, and low-risk, based on hypotension, RV dysfunction, and/or cardiac biomarkers [1].

Definition of Risk Stratification

High-risk (massive) PTE: patients with shock or hypotension (systolic blood pressure <90 mmHg or decrease in systolic blood pressure of ≥40 mmHg from baseline) and RV dysfunction. These patients account for less than 5% of acute PTE cases [14]. Early hospital mortality in hypotensive PTE cases varies between 25% and 65% [1].

Intermediate-risk (submassive) PTE: patients without shock or hypotension but with signs of RV dysfunction and/or positive cardiac biomarkers or sPESI >1. The mortality rate in this group is 5%-15% [3].

Low-risk (nonmassive) PTE: patients without shock/hypotension and no signs of RV dysfunction or with sPESI <1. The early mortality rate in this group is below 1% [3].

In this review, we will talk about thrombolytic therapy, which is the primary treatment for patients with especially life-threatening high-risk PTE and recent developments in this area.

Thrombolytic Therapy

Thrombolytic drugs are agents that actively dissolve the thrombus by converting plasminogen into plasmin. With early thrombus resolution, the elevated pulmonary arterial pressure/resistance and accompanying RV dysfunction improve rapidly. Thrombus resolution within the first 24 hours in particular is much faster in thrombolytic therapy than with heparin [1, 3].

PTE with hemodynamic instability accounts for 5%-10% of PTE cases [15, 16]. RV dysfunction is detected in 30%–50% of PTE cases. Both parameters indicate poor prognosis [12, 13, 16].

Thrombolytic therapy leads to early normalization of both hemodynamic parameters and RV function, thus reducing mortality. However, its effects on long-term mortality and prognosis are controversial [17]. Furthermore, the increased risk of major hemorrhage must also be taken into consideration.

Indications

The main indication for thrombolysis is high-risk PTE with otherwise unexplainable shock and/or persistent hypotension [1, 3, 18]. In a meta-analysis, a subgroup analysis of patients with massive PTE demonstrated that thrombolytic therapy reduced mortality and recurrence [19].

For intermediate-/high-risk patients (those with severe hypoxemia, diffuse perfusion defect, severe or worsening RV dysfunction, PTE-related cardiopulmonary arrest, free thrombus in the right atrium or ventricle, and/or foramen ovale opening) without hypotension or shock, thrombolytic therapy is recommended if there is a low risk of bleeding [3, 18]. The indications for thrombolytic therapy are summarized in Table 1.

Thrombolysis is most controversial for the intermediate-risk group [10]. Numerous studies have shown that thrombolytic agents improve RV dysfunction, and a meta-analysis revealed a survival advantage [20-24]. The largest of these studies is the Pulmonary Embolism Thrombolysis Study. Tenecteplase + heparin was compared with placebo + heparin in this multicenter, double-blind, randomized controlled study. It was found that thrombolytic therapy did not significantly reduce mortality in the first 7 or 30 days, but that it prevented hemodynamic deterioration. However, major bleeding was significantly more common in the tenecteplase group [21]. Another randomized study compared low-molecular weight heparin (LMWH) and LMWH + tenecteplase. At 3-month follow-up, the tenecteplase group showed a better prognosis, quality of life, and functional capacity [25].

Extensive clot burden can increase pulmonary arterial pressure without causing hemodynamic collapse or RV dysfunction. In a large retrospective study, it was shown that in acute PTE, a CTA obstruction index >40% was associated with an 11-fold increase in mortality [26]. However, a recent review stated that there is insufficient evidence to conclude that systemic thrombolysis reduces mortality with an acceptable hemorrhage incidence [27].

Data on the use of thrombolytics in patients with severe hypoxemia, PTE-related cardiopulmonary arrest, and free thrombus in the right ventricle or atrium are limited, and a case-based approach is recommended [27].

Table 1. Indications of thrombolytic treatment in acute pulmonary thromboembolism

Absolute indication	Possible indication
High-risk (massive) PTE	Intermediate-risk (submassive) PTE*
(presence of hypotension related to PTE)	Presence of severe hypoxemia
	Severe or worsening right ventricular dysfunction
	Patients with acute PE who appear to be decompensating (e.g., elevated cardiac biomarkers, increasing tachycardia)
	Free-floating thrombus in right atrial or ventricular
	Extensive clot burden

*If include one of these criteria; PTE: pulmonary thromboembolism

Table 2. Contraindications of thrombolytic treatment in acute pulmonary thromboembolism

Absolute contraindications	Relative contraindications
Prior intracranial hemorrhage	Severe uncontrolled hypertension on presentation (SBP>180 mmHg or DBP>110 mmHg)
Known structural cerebral vascular lesion	History of ischemic stroke more than 3 months before
Known malignant intracranial neoplasm	Major surgery less than 3 weeks before
Ischemic stroke within 3 months	Recent (within 2 to 4 weeks) internal bleeding
Active bleeding (excluding menses)	Noncompressible vascular punctures
Significant closed-head trauma or facial trauma within 3 months	Current use of an anticoagulant that produced an elevated INR>1.7 or PT>15 seconds
	Pregnancy
	Recent invasive procedure
	Active peptic ulcer
	Pericarditis or pericardial fluid
	Age >75 years
	Diabetic retinopathy

SBP: systolic blood pressure; DBP: diastolic blood pressure; INR: international normalized ratio; PT: prothrombin time

Table 3. Systemic routes of administration of thrombolytic drugs

Drug name	Loading dose	Infusion dose	Administration time
Streptokinase	250000 IU, 30 min	100000 IU/h	24 h
Urokinase	4400 IU, 10 min	4400 IU/kg/h	12 h
Alteplase (rt-PA)	Not needed	50 mg/h*	2 h
Reteplase	Not needed	10 U IV bolus, twice with 30-min interval	
Tenecteplase	Not needed	10000 U bolus single dose in 5-10 seconds**	

*For patients below 65 kg, total dose in 2 h is calculated as 1.5 mg/kg
**Should be administered based on body weight with maximum dose of 50 mg (10000 U tenecteplase)

Thrombolytic therapy is effective if applied within the first 48 hours of symptom onset. Its efficacy decreases significantly after 7 days, but it may be beneficial up to 14 days from symptom onset [3].

Contraindications

Absolute and relative contraindications of thrombolytic therapy are presented in Table 2. Particularly in relative contraindications, treatment decisions must be made considering the risk-benefit balance. Absolute contraindications can be relative in life-threatening high-risk PTE. Intracranial events in particular should be assessed meticulously. Thrombolytic therapy can moderately increase bleeding in menstruating women, but major hemorrhage is rare. Thus, menstruation is not a contraindication for thrombolytic therapy. Although the risk of maternal hemorrhage is high in pregnancy, a thrombolytic should be used in high-risk embolism patients.

Thrombolytic Agents

Thrombolytic agents have been used in the treatment of PTE for nearly half a century. The most prominent of these agents are streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA, alteplase). Miller et al. [28] first demonstrated the effectiveness of streptokinase in PTE in 1971, which was followed by similar demonstrations with other agents in numerous randomized controlled studies [29-31]. Other thrombolytic agents include lenoteplase, tenecteplase, and reteplase, but the most commonly used drug today is rt-PA. Systemic administration routes of thrombolytic drugs are summarized in Table 3.

Streptokinase

This polypeptide is obtained from group C ß hemolytic streptococci. It binds to plasminogen and the resulting complex induces conversion of plasminogen to plasmin. The presence of fibrin does not enhance its activity. Although it is the cheapest fibrinolytic agent, it has more side effects, such as allergic reaction and hypotension. Due to its antigenic structure, it cannot be safely re-administered for at least 6 months. It has a half-life of up to 83 minutes [32].

Urokinase

This agent is physiologically secreted from renal parenchymal cells and can be obtained from human urine, human embryos, and kidney cell cultures. It is usually used for catheter obstructions in interventional radiology. Its half-life is 20 minutes. Moreover, it does not have an antigenic structure and can be re-administered if required [33].

Alteplase (rt-PA)

This is the first recombinant tissue plasminogen activator. It is synthesized in the tissue by the venous endothelium. It is fibrin-specific and becomes active after binding to fibrin. However, it also leads to the risk of systemic bleeding. It has a half-life of 4–6 minutes. After the 2-hour administration of rt-PA, pulmonary arterial pressure is reduced by a mean of 30%, and cardiac index increases by 15% [18].

Reteplase

It is a second-generation tissue plasminogen activator produced in *Escherichia coli* using recombinant DNA techniques. Its half-life is 13–16 minutes, and it is administered by bolus. It does not have an antigenic structure and can be re-administered if required [34]. It is not approved by the FDA for indications other than acute myocardial infarction. However, it is used in deep vein thrombosis and PTE worldwide, including in Turkey.

Tenecteplase

Tenecteplase is produced in a Chinese hamster ovary cell line using the recombinant DNA technology. It is indicated in the treatment of acute myocardial infarction [35]. Its half-life is 20–24 minutes. Clinical studies on its use in PTE are ongoing.

Thrombolytic Drugs and Anticoagulation

Anticoagulation must be discontinued when thrombolytic therapy is administered, especially if using streptokinase or urokinase. This is not an absolute requirement for rt-PA.

If standard heparin (SH) therapy was initiated and suspended during thrombolytic therapy, it should be resumed after completing the thrombolytic infusion and checking activated partial thromboplastin time (aPTT). Checking aPTT is not necessary for patients who were not started on SH therapy. If aPTT is less than twice the normal upper limit (<80 s), SH is resumed at 18 IU/kg/h without a loading dose. If aPTT is still >80 s, measurement should be repeated every 4 hours, and SH therapy should be resumed when it reaches <80 s. For patients who were treated with LMWH prior to thrombolytic therapy, SH infusion is initiated after 12 or 24 hours depending on the type of LMWH (administered every 12 or 24 hours, respectively). Although there are some studies indicating that anticoagulation with LWMH can be continued after thrombolytic therapy, it has not yet been included in the guidelines [9, 36, 37]. These studies showed that thrombolytic therapy + LWMH was as effective as thrombolytic therapy + SH with a lower bleeding risk in the LMWH group, although the difference was not statistically significant [36, 37].

Low-Dose rt-PA

Alteplase (rt-PA) is still the most commonly used thrombolytic agent in pulmonary embolism. The approved dose for PTE is infusion of 100 mg in 2 hours. This dose is known to cause major bleeding complications (primarily cerebral hemorrhage), especially in older patients. Therefore, recent studies have demonstrated that low-dose rt-PA (0.6 mg/kg, maximum 50 mg/2 hours) is as effective as the standard dose and much safer in terms of bleeding [38-40]. A recent meta-analysis evaluating four studies that compared low-dose and standard-dose alteplase revealed no difference in mortality between the two arms of treatment and a lower incidence of major bleeding with low-dose therapy, although the difference was not statistically significant [41]. Moreover, a retrospective study on the long-term outcomes of low-dose rt-PA reported similar outcomes to those with the standard dose [42]. These results suggest that low-dose therapy can be considered as a first-line alternative in patients with intermediate-risk PTE. However, larger prospective studies are required. In addition, findings that rt-PA at a low-dose is as effective as the standard dose raises several questions that must be answered. Can the dose of systemic thrombolytic be reduced any further? Can the dose be adjusted based on improvement of clinical parameters? In this way, can the risk of hemorrhage be further reduced?

Catheter-Directed Thrombolysis

In this type of treatment, thrombolytic agents can be administered directly to the pulmonary artery via catheter [22, 43-45]. Catheter-directed thrombolysis (CDT) should be performed in centers with expertise in this area. The potential advantage of CDT is that a lower dose of the lytic agent is administered, resulting in a lower risk of bleeding compared to systemic treatment. The most studied form of CDT is ultrasound-assisted thrombolysis (USAT) [46]. In this method, a specific catheter that includes an ultrasound transducer aims to disrupt the clot ultrastructure, increasing penetration of the thrombolytic into the clot. Sharifi et al. [47] recently conducted a study retrospectively comparing half-dose thrombolytic and USAT. They reported a significant decrease in systolic pulmonary arterial pressure and the RV/LV ratio in both treatment arms. However, the decrease was greater with half-dose thrombolysis. In addition, these improvements were achieved in a shorter time and at lower cost in the half-dose thrombolysis group [47]. Similarly, recent guidelines have emphasized the cost and need for experience in performing CDT. Guidelines recommend CDT as an alternative to surgical embolectomy for patients who did not respond to systemic thrombolysis, who are at risk of death before systemic thrombolysis takes effect, and those with contraindications for systemic thrombolysis [3, 18]. However, it must be kept in mind that CDT cannot be implemented faster than systemic thrombolysis.

Complications

The complications of thrombolytic therapy can be summarized as bleeding, allergic reactions (especially when using streptokinase), embolism, stroke, and reperfusion arrhythmias.

The most important complication and contraindication of this therapy is bleeding, especially intracranial hemorrhage. The risk of bleeding increases with aneurysm, tumor, infarction, trauma, or surgical intervention in the cerebral system, advanced age, uncontrolled hypertension, bleeding diathesis, low body weight, and severe heart disease. In the literature, the prevalence of major hemorrhage (requiring discontinuation of treatment and >2 units of blood transfusion within 24 hours) varies between 2% and 28% [36, 48-50].

The incidence of hemorrhage due to thrombolytic therapy has clearly decreased from past to present. Factors leading to this decrease include careful patient selection, improved patient care facilities, and avoidance of invasive diagnostic procedures that require catheterization by arterial and large vein puncture (such as conventional pulmonary angiography) in patients scheduled for thrombolytic therapy.

If bleeding from the venous entry port occurs, applying pressure to the area will effectively stop the bleeding. For severe bleeding, however, drug discontinuation should be the first course of action, and it is usually adequate to achieve hemostasis. Massive and continuous bleeding is managed with cryoprecipitate infusion. If this is insufficient, the patient is given fresh frozen plasma, thrombocyte suspension, and antifibrinolytic drugs [51].

Conclusion

Systemic thrombolytic therapy should be the first choice in patients with high-risk PTE. CDT may be an alternative for patients not eligible for systemic thrombolytic therapy. Administering systemic thrombolytic therapy to patients with intermediate-risk PTE remains controversial. Low-dose rt-PA seems to be a possible alternative in this group.

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