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Does Fibrinolytic Strategy of Pulmonary Embolism International THrOmbolysis (PEITHO)-3 Trial Need More Strong Evidence?

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We have recently read with great interest the article by Sanchez et al entitled "Reduced-dose intravenous thrombolysis for acute intermediate-high-risk pulmonary embolism: rationale and design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial."[1] We congratulate the authors for their article describing the rationale and design of the PEITHO-3 trial. However, we would like to present a different perspective in the light of current evidence regarding thrombolytic strategies for acute intermediate-high-risk pulmonary embolism (PE).

Potential hemodynamic and clinical benefits of fibrinolytic therapy (FT) in the management of submassive patients have been previously established.[2–6] FT is a "double-edged sword"; its clinical efficacy has been provided in the seemingly integral "cost" of bleeding complications specific to the induction of a systemic lytic condition.[7] However, tissue plasminogen activator (t-PA) is used as an acceptable therapeutic agent in patients with PE that causes hemodynamic deterioration, even if there is a risk of major bleeding (including intracranial) due to its nature.[7] On the other hand, accelerated systemic FT (100 mg t-PA in 2 hours) in intermediate-high-risk PE reduces the incidence of hemodynamic impairment, but the benefit of mortality has not been proven yet and is associated with a 10% risk of major bleeding.[3,8] Major cardiovascular guidelines regarding PE have considered full-dose systemic fibrinolysis as class 3 indication for submassive PE.[7] Various alternative strategies have been designed to reduce bleeding complications without loss of efficacy.

In 1990, Levine et al, in a randomized clinical trial (RCT) with a limited number of patients (33 patients), adopted 2-minute t-PA 0.6 mg/kg for FT in the intervention arm of the trial for patients with acute symptomatic PE.[9] They indicated that a bolus regimen of t-PA produces accelerated fibrinolysis and provides an alternative and convenient approach to FT in patients with PE. Recently, in a prospective study, Yilmaz and Uzun demonstrated significant elimination of major bleeding complications, along with optimal clinical outcomes using a half-dose fibrinolysis strategy (50 mg/2 h).[4] Moreover, Rothschild et al reported risks of major bleeding (11%) and 30-day mortality (4.4%) involved with the application of half-dose systemic FT against acute submassive PE, similar to a previous study on systemic FT.[3] Interestingly, Sharifi et al showed good clinical outcomes and no bleeding in patients with submassive PE using a different half-dose FT strategy, which involved the administration of 10 mg bolus IV (intravenous) within 1 minute followed by 40-mg bolus IV infusion within 2 hours.[2] Considering the evidence regarding systemic FT, use of this therapeutically effective systemic drug seems to be correlated with significant bleeding risks, regardless of the administration route or dose. The readers may wonder why the half-dose treatment strategy with a 2-hour infusion time with stronger evidence was not chosen in this RCT.

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