Chula Med J Vol. 58 No. 6 November- December 2014

Thrombolytic therapy in patients with submassive pulmonary embolism: A systematic review

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Kittinaradorn D, Tangnuntachai N, Wongjarupong N, Longchit D, Atipookanok S, Boondarikpornpant T, Nopmaneepaisarn T, Papassornsiri T, Soopanit T, Tantirungsi T, Supakmontri T, Rattanaphong T, Suksirivoraboot T, Pachinburavan M, Katavetin P. Thrombolytic therapy in patients with submassive pulmonary embolism: A systematic review. Chula Med J 2014 Nov – Dec; 58(6): 589 - 97

Background : *The use of thrombolytic therapy in patients with submassive pulmonary embolism (PE) is still controversial.*

Objective : *To evaluate the role of thrombolytic therapy in patients with submassive PE.*

Design : *Systematic review.*

Setting : *Faculty of Medicine, Chulalongkorn University.*

Methods : *We performed a literature search using Pubmed, Scopus, scientific abstracts from meetings, and bibliographies of retrieved articles. Only randomized control trials were included in this systematic review.*

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Result : *Three randomized control trials were identified. All these studies excluded patients with high risk of bleeding. The evidence from randomized control trials identified in this systematic review suggested that thrombolytic therapy in addition to heparin may provide a long-term mortality benefit, prevent clinical deterioration, and preserve right ventricular function with a slightly increased risk of minor bleeding in patients with submassive PE. The benefits of thrombolytic therapy were most obvious in a randomized control trial that enrolled patients within 6 hours after the onset of the symptoms.*

Conclusion : *Thrombolytic therapy may be considered in patients with submassive PE who have low risk of bleeding complications and present early after the onset of the symptoms.*

Keywords : *Thrombolysis, alteplase, submassive PE, right ventricular dysfunction.*

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Received for publication. February 12, 2014.

ดนยา กิตตินราดร, ณิชธิดา ตั้งนันทชัย, ณิชา วงษ์จารุพงษ์, ดวงทิพย์ หลงจิตร, ทรงภูมิ อธิภูกนก, ทศพร บุญฑริกพรพันธุ์, ทิตพร นพมณีไพศาล, ทิพย์ญาดา ปภัสสรศิริ, ธณิอร ศุภนิตย์, ธนบูรณ์ ตันติรังสี, ธนภัทร สุพักตร์มนตรี, ธนวดี รัตนพงษ์, ธนวินทร์ สุขสิริวรบุตร, มนวสี ปาจีนบูรวรรณ์, พิสุทธิ์ กตเวทิน. **การให้ยาละลายลิ่มเลือดในผู้ป่วยที่มีลิ่มเลือดอุดตันในหลอดเลือดปอดแบบกึ่งรุนแรง: การทบทวนวรรณกรรมอย่างเป็นระบบ. จุฬาลงกรณ์เวชสาร 2557 พ.ย. – ธ.ค.; 58(6): 589 – 97**

ที่มา : *ในปัจจุบันยังมีการถกเถียงกันเกี่ยวกับการรักษาด้วยยาละลายลิ่มเลือดในผู้ป่วยที่มีลิ่มเลือดอุดตันในหลอดเลือดแดงปอดแบบกึ่งรุนแรง*

วัตถุประสงค์ : *เพื่อวิเคราะห์ผลของการให้ยาละลายลิ่มเลือดในผู้ป่วยที่มีลิ่มเลือดอุดตันในหลอดเลือดแดงปอดแบบกึ่งรุนแรง*

รูปแบบการวิจัย : *การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมาน*

สถานที่ทำการวิจัย : *คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

วิธีการศึกษา : *ทำการค้นหารายงานการศึกษาแบบทดลองทางคลินิกแบบสุ่ม และมีกลุ่มควบคุมจากฐานข้อมูลพับเมด สโคปัส บทคัดย่อของการประชุมวิชาการ และเอกสารอ้างอิงจากรายงานต่าง ๆ ที่หามาได้*

ผลการศึกษา : *พบรายงานการศึกษาแบบทดลองทางคลินิกแบบสุ่มและมีกลุ่มควบคุม 3 การศึกษา ทุกการศึกษาไม่นำผู้ป่วยที่มีความเสี่ยงสูงต่อภาวะเลือดออกรุนแรงเข้าในการศึกษา ข้อมูลจากการศึกษาแบบทดลองทางคลินิกแบบสุ่ม และมีกลุ่มควบคุมที่พบในการทบทวนวรรณกรรมอย่างเป็นระบบนี้ บ่งชี้ว่าการให้ยาละลายลิ่มเลือดในผู้ป่วยที่มีลิ่มเลือดอุดตันในหลอดเลือดปอดแบบกึ่งรุนแรงอาจช่วยลดอัตราตายในระยะยาวได้ป้องกันการดำเนินโรคที่แย่ลง และช่วยรักษาการทำงานของหัวใจห้องล่างขวาได้ ในขณะที่มีความเสี่ยงเรื่องเลือดออกแบบไม่รุนแรงเพิ่มขึ้นเล็กน้อย การศึกษาที่เห็นผลดีของการให้ยาละลายลิ่มเลือดชัดที่สุดคือการศึกษาที่เริ่มให้ยาภายในระยะเวลา 6 ชั่วโมงหลังจากเริ่มมีอาการ*

สรุป : *การให้ยาละลายลิ่มเลือดในผู้ป่วยที่มีลิ่มเลือดอุดตันในหลอดเลือดปอดแบบกึ่งรุนแรงอาจพิจารณาให้ได้ในผู้ป่วย ซึ่งไม่มีความเสี่ยงสูงต่อภาวะเลือดออกรุนแรงและมาถึงโรงพยาบาลอย่างรวดเร็วหลังจากมีอาการ*

คำสำคัญ : *ยาละลายลิ่มเลือด, ลิ่มเลือดอุดตันในปอด, การทำงานของหัวใจห้องล่างขวา.*

The leading case

A 58-year-old woman with history of cigarette smoking presented with sudden onset of right-sided chest discomfort and dyspnea 2 hours prior to her visit to the emergency room. On the initial physical examination, her heart rate was 110 beats per minute; blood pressure 128/72 mm Hg; respiratory rate 24 breaths per minute, and oxygen saturation at room air 88%. Jugular veins were distended. Holosystolic murmur grade 3/6 was detected at the left lower sternal border. Lung examination revealed equal breath sounds without any adventitious resonance. Symmetrical lower-extremity pitting edema was also noted. The ECG was notable for sinus tachycardia and T-wave inversions across the anterior precordium. Laboratory evaluation was remarkable for a D-dimer level of 1,104 ng/mL (normal <500 ng/mL) and a cardiac troponin I level of 1.4 ng/mL (normal <0.1 ng/mL). Contrast-enhanced chest computed tomography demonstrated thrombus that filled the right main pulmonary artery and moderate right ventricular (RV) enlargement (RV-to-left ventricular [LV] dimension ratio = 1.2). Bedside transthoracic echocardiography also documented moderately severe RV hypokinesis, moderate tricuspid regurgitation, and an estimated pulmonary artery systolic pressure of 55 mm Hg. These clinical, laboratory, and imaging findings established the diagnosis of submassive acute pulmonary embolism (PE).

The question is: Should this patient receive thrombolytic therapy?

Introduction

Acute pulmonary embolism (PE) is a common life-threatening disease caused by materials (e.g. thrombus, tumor, air, or fat) that can be originated from anywhere in the body to lodge and obstruct the pulmonary artery or one of its branches.[1]

The appropriate treatment for PE depends largely on the severity of the disease that hence affects the risk of adverse clinical outcome; On one hand, patients with hemodynamic instability due to the confirmed massive PE should be treated with either thrombolytic therapy (plus anticoagulation) or embolectomy; on the other hand, patients with low-risk PE who have only minor hemodynamic disturbance (no right ventricular dysfunction) could be treated with anticoagulant therapy alone (unfractionated heparin, low molecular weight heparin, or warfarin). However, the appropriate management for those in the middle clinical spectrum of PE collectively called submassive PE, such as those who have right ventricular dysfunction without hypotension as in the leading case, remains controversial.[2-4]

The objective of the present systematic review is to evaluate the role of thrombolytic therapy in patients with submassive PE.

Methods

The Literature Search

We searched Pubmed and Scopus with the relevant searching terms (Table 1). The conference abstracts of American thoracic society and Thai thoracic society were also searched. We also hand-searched the reference list of every primary study for additional publications. A total of 229 non-duplicated articles was identified.

Table 1. The search terms for Pubmed and Scopus.

The search term for Pubmed(Thromboly*[Title/Abstract] OR Fibrinoly*[Title/Abstract] OR Rtpa[Title/Abstract] OR Recombinant tissue plasminogen activator[Title/Abstract] OR Streptokinase[Title/Abstract] OR Urokinase[Title/Abstract] AND (submassive[Title/Abstract] OR Right ventricular dysfunction[Title/Abstract] OR Myocardial necrosis[Title/Abstract])) AND pulmonary embolism[Title/Abstract]
The search term for Scopus(TITLE-ABS-KEY(thromboly) OR TITLE-ABS-KEY(fibrinoly) OR TITLE-ABS-KEY(rtpa) OR TITLE-ABS-KEY(recombinant tissue plasminogen activator) OR TITLE-ABS-KEY(urokinase) OR TITLE-ABS-KEY(streptokinase)) AND (TITLE-ABS-KEY(submassive) OR TITLE-ABS-KEY(right ventricular dysfunction) OR TITLE-ABS-KEY(myocardial necrosis)) AND TITLE-ABS-KEY(pulmonary embolism)

Data collection process

The titles and abstracts of 229 studies were read by two authors to select the articles for further review according to the pre-specified protocol. The clinical trials that compared right ventricular function, mortality and rate of recurrent PE between thrombolytic plus heparin and heparin-alone in submassive PE patients were included for further review. The studies that had the number of subject of less than 10 in each group, used non-English language, and included other co-interventions, such as embolectomy, were excluded.

The two authors extracted and reviewed data separately, and if there were any controversial findings, the third author would make a decision. A total of 213 articles were excluded. We then reviewed the full-text of the remaining 16 articles. Thirteen articles were further excluded: 6 studies other than clinical trials, 4 languages other than English, 2 unclearly separated results of massive and submassive PE, and 1 irrelevant outcomes. We finally had 3 studies included in the present systematic review.

Results

Three randomized control trials were identified in this systematic review.[5 - 7] The study design and the study validity are summarized in Table 2 and 3. Outcomes of the thrombolytic therapy in submassive PE are summarized in Table 4 and discussed in details below. The meta-analysis could not be performed because these studies examined different outcomes.

A. Mortality

Fasullo *et al.* reported that thrombolytic therapy in a conjunction with heparin resulted in a statistically significant decrease in mortality over 6 months compared with heparin alone, while Konstantinides *et al.* found no significant differences in in-hospital mortality between the two groups.[6 - 7] Factors that may explain the discrepancy between these two studies are the difference in observation period (6 months *versus* within 30 days) and the timing of thrombolytic therapy (within 6 hours after the onset of the symptoms versus within 2 - 4 days). Therefore, the thrombolytic therapy might have a long-term mortality benefit when it was administered early within

6 hours after the onset of the symptoms. The other factors that may explain the discrepancy between these studies is the higher mortality rate of the heparin group in Fasullo *et al.* which might be caused by the absent of escalation protocol and larger percentage of patients with echocardiographic evidence of right ventricular dysfunction in this study.

Table 2. The P-I-C-O summary of randomized controlled trials.

PICO	Goldhaber et al. (1993)[5]	Konstantinides et al. (2002)[6]	Fasullo et al. (2011)[7]
Patients	36 submassive PE patients * Age: >18 years old Timing: within 14 days Exclude high risk of bleeding	256 submassive PE patients Age: <80 years old Timing: within 96 hrs Exclude high risk of bleeding	76 submassive PE patients Age: 18 – 75 years old Timing: within 6 hrs Exclude high risk of bleeding
Intervention	Alteplase 100 mg IV of in 2 hrs	Alteplase 10 mg IV bolus then 90 mg IV in 2 hrs	Alteplase 10 mg IV bolus then 90 mg IV in 2 hrs
Control	Heparin 5,000 U IV bolus	Placebo	Placebo
Co-intervention (Both groups)	Heparin infusion 1000 U/hr (adjusted dose according to target aPTT) then switched to warfarin	Heparin 5,000 U IV bolus then heparin infusion 1000 U/hr (adjusted dose according to target aPTT) then switched to warfarin	
Outcomes	Right ventricular function at 3 and 24hr Other outcomes are not available for submassive PE subgroup	Death and recurrent PE during hospital stay or 30 days after randomization Escalation of treatment during hospital stay or 30 days after randomization Major bleeding events during hospital stay or 30 days after randomization	Right ventricular function at 24, 48, 72 hours, 6 days, discharge, 3 months, and 6 months Death and recurrent PE within 6 months Major bleeding events within 6 months

* Only subgroup with submassive PE included in the present systematic review

Table 3. The study validity of the randomized controlled trials.

Criteria	Goldhaber et al. (1993)[5]	Konstantinides et al. (2002)[6]	Fasullo et al. (2011)[7]
Randomization	Yes	Yes	Yes
Concealment	Adequate	Adequate	Adequate
Blinding	None	Double-blind	Double-blind
Follow-up	Complete	Complete	Complete
Baseline comparison	Similar	Similar	Similar
Intention-to-treat analysis	Yes	Yes	Yes

Table 4. The outcomes of the thrombolytic therapy in the randomized controlled trials.

Outcomes	Goldhaber et al. (1993)[5] *			Konstantinides et al. (2002)[6]			Fasullo et al. (2011)[7]		
	Thrombolysis	Heparin	p-value	Thrombolysis	Heparin	p-value	Thrombolysis	Heparin	p-value
Death	N/A	N/A	N/A	4/118 (3.4%)	3/138 (2.2%)	0.71	0/37 (0%)	6/35 (17.1%)	0.03
Escalation of treatment	N/A	N/A	N/A	12/118 (10.2%)	34/138 (24.6%)	0.004	N/A	N/A	N/A
Persistent or worsening RV dysfunction	2/18 (11.1%)	12/18 (66.7%)	0.01	N/A	N/A	N/A	0/37 (0%)	5/35 (14.3%)	0.02
Recurrent PE	N/A	N/A	N/A	4/118 (3.4%)	4/138 (2.9%)	0.89	0/37 (0%)	1/35 (2.9%)	0.49
Major bleeding	N/A	N/A	N/A	1/118 (0.8%)	5/138 (3.6%)	0.29	2/37 (5.4)	1/35 (2.9%)	1.00
Minor bleeding	N/A	N/A	N/A	N/A	N/A	N/A	16/37 (43.2%)	8/35 (22%)	0.08

* Only subgroup with submassive PE included in the present systematic review

B. Escalation of treatment

The escalation of treatment was defined as the use of at least one of the following: infusion of a catecholamine because of persistent arterial hypotension or shock; secondary, or "rescue," thrombolysis; endotracheal intubation; cardio-pulmonary resuscitation; and emergency surgical embolectomy or thrombus fragmentation by catheter.[6] Konstantinides *et al.* found that thrombolytic therapy in conjunction with heparin had the significantly lower the rate of escalation of treatment than heparin alone.[6] This finding suggests that thrombolytic therapy may prevent clinical deterioration requiring treatment escalation in patients with submassive PE.

C. Recurrent PE

There were no statistically significant differences in the rate of recurrent PE between thrombotytic therapy in conjunction with heparin and heparin alone.

D. Right ventricular (RV) dysfunction

In the subgroup of submassive PE patients, Goldhaber *et al.* demonstrated that thrombolytic therapy in conjunction with heparin reduced the rate of persistent RV dysfunction compared with heparin alone.[5] Fasullo *et al.* also reported a lower rate of persistent or worsening RV dysfunction in thrombolytic group compared with heparin group.[7] In the latter study, the echocardiographic outcomes, such as paradoxical systolic septal motion, tricuspid annular plane systolic excursion, and pulmonary hypertension, were comprehensively evaluated at baseline, 24 hours, 48 hours, 72 hours, 6 days, discharge, 3 months, 6 months after randomization. The thrombolysis group had significantly better echocardiographic parameters than the heparin group.[7]

E. Bleeding complications

Major bleeding, such as fatal bleeding, intracranial bleeding, and bleeding that require red-cell transfusion, were not significantly different between thrombolytic group and heparin group.[6 - 7] Fasullo *et al.* also reported an increase of minor bleedings. The patients receiving thrombolytic therapy in conjunction with heparin had higher number of minor bleedings than patients receiving heparin alone.[7]

Discussion

The evidence from randomized control trials identified in this systematic review suggested that the thrombolytic therapy in addition to heparin in patients with submassive PE may provide a long-term mortality benefit, prevent clinical deterioration, and preserve right ventricular function, especially when it is initiated early within 6 hours after the onset of the symptoms. The thrombolytic therapy does not increase major bleeding complications in patients without high risk of bleeding, although it increases minor bleeding events. Therefore, thrombolytic therapy may be considered in patients with submassive PE who have low risks of bleeding and present early within 6 hours after onset of the symptoms.

However, data from only a few randomized control trials are not sufficient to make an evidence-based recommendation. Further studies in patients with submassive PE are therefore warranted.

In the literature search, we found an ongoing prospective randomized control trial comparing thrombolytic therapy using tenecteplase *versus* placebo in submassive PE, the PEITHO (Pulmonary EmboIism THrombolysis) trial.[8] This study is expected to enroll about 1,000 patients. The result of this study would provide us an effective conclusion regarding the clinical benefits of thrombolytic therapy in patients with submassive PE.

Back to the leading case, a 58-year-old woman presented with sudden onset of right-sided chest discomfort and dyspnea 2 hours prior to her visit to the emergency room. This patient had submassive PE with low risk for bleeding (no history of prior GI bleeding, intracranial bleeding, recent surgery and trauma) and presented early (within 6 hours after the onset of symptoms). Thus, we suggest that this patient should be offered thrombolytic therapy in her initial treatment along with anticoagulant.

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