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Thrombolysis Versus Anticoagulation for the Initial Treatment of Moderate Pulmonary Embolism: A Meta-Analysis of Randomized Controlled Trials

Hong Chen MD, Cheng Ren MD, and Hong Chen MD PhD

BACKGROUND: Randomized trials and meta-analyses have reached conflicting conclusions regarding the risk benefit ratio of thrombolytic therapy or anticoagulant therapy in patients with moderate pulmonary embolism. To investigate the effect of initial thrombolysis and anticoagulant therapy in patients with moderate pulmonary embolism, we performed an updated meta-analysis. METHODS: We searched the MEDLINE, Embase, Cochrane Library, Wanfang, and CNKI databases for randomized controlled trials focusing on moderate pulmonary embolism. We then performed a meta-analysis of all randomized trials comparing thrombolytic therapy with heparin treatment in subjects with moderate pulmonary embolism. RESULTS: Fifteen trials involving 1,247 subjects were included. Compared with anticoagulation, thrombolytic therapy was associated with a significant reduction in recurrent pulmonary embolism or death (1.94% vs 5.87%, odds ratio (OR) of 0.37, 95% CI 0.21–0.66, *P* for heterogeneity = .49), a nonsignificant increase in major bleeding (3.57% vs 2.67%, OR 1.34, 95% CI 0.70–2.58), and a significant increase in non-major bleeding (12.78% vs 3.65%, OR 4.12, 95% CI 2.37–7.17). Thrombolysis was associated with a significant reduction in recurrent pulmonary embolism or death in trials that enrolled both foreign subjects (3.46% vs 7.76%, OR 0.45, 95% CI 0.23–0.86) and Chinese subjects (0.00% vs 3.72%, OR 0.18, 95% CI 0.05–0.73). With regard to moderate pulmonary embolism, comparison of thrombolysis and anticoagulation showed a nonsignificant heterogeneity between the 2 trial groups (*P* = .12). CONCLUSIONS: Both mortality and pulmonary embolism recurrence are decreased with thrombolysis compared with heparin treatment in patients with moderate pulmonary embolism. The risk of non-major bleeding is increased, but the risk of major bleeding is not.
Key words: pulmonary embolism; thrombolysis; heparin; meta-analysis. [Respir Care 2014;59(12):1–•. © 2014 Daedalus Enterprises]

Introduction

Pulmonary embolism is a life-threatening disease, with an estimated incidence of 6–7/10,000 people, and it is associated with a 3-month mortality rate of up to 17%.[1,2] To date, the use of thrombolysis is recommend only in patients with massive pulmonary embolism. Moderate pulmonary embolism is a defined subgroup of pulmonary embolism, in which patients have hemodynamic stability but with right ventricular enlargement or hypokinesia or elevation of biomarkers of right ventricular injury. The initial treatment of moderate pulmonary embolism with thrombolytic therapy or anticoagulation has been under dispute for > 3 decades. The principal contradiction comes from different risk benefit ratios of treatment with thrombolytic therapy or anticoagulant therapy in randomized controlled trials (RCTs). The interpretation of meta-analyses[3-6] showed that thrombolytic therapy in patients with moderate pulmonary embolism does not reduce mortality or recurrence rate. However, these previous meta-analyses included a few RCTs that were small sample studies and appear to be of limited value in guiding clin-

The authors are affiliated with the Department of Respiratory Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. Hong Chen MD is also affiliated with the Department of Respiratory Medicine, The People's Hospital of Yubei, District of Chongqing City, Chongqing, China.

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Correspondence: Hong Chen MD PhD, Department of Respiratory Medicine, First Affiliated Hospital of Chongqing Medical University, No. 1, Yixue Road, Yuzhong District, Chongqing 400016, China. E-mail: hopehong2003@126.com.

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ical treatment. The recently published RCTs showed reduction in recurrent pulmonary embolism or death with thrombolysis compared with anticoagulant therapy. To investigate the benefits of thrombolysis in moderate pulmonary embolism, we performed an updated meta-analysis of RCTs comparing thrombolysis and anticoagulation in subjects with moderate pulmonary embolism.

QUICK LOOK

Current knowledge

In patients with moderate pulmonary embolism, conflicting conclusions have been reached regarding the risk-benefit ratio of thrombolytic therapy to anticoagulant therapy in randomized trials and meta-analyses.

What this paper contributes to our knowledge

Compared with heparin, both mortality and pulmonary embolism recurrence are decreased by thrombolysis in patients with moderate pulmonary embolism. The risk of non-major bleeding increases, but the risk of major bleeding does not increase.

Methods

Study Identification

We attempted to identify all relevant published RCTs comparing thrombolytic therapy and anticoagulant therapy for the initial treatment of moderate pulmonary embolism. We searched the MEDLINE and Embase databases from January 1980 to June 2013 and the Cochrane Library, Wanfang, and CNKI databases from January 1990 to June 2013 using the terms pulmonary embolism, thromboembolism, thrombolysis, fibrinolysis, recombinant tissue plasminogen activator, rt-PA, alteplase, randomized controlled trial, controlled clinical trial, and humans. We also searched references cited in journal articles.

Study Selection

Two investigators (Hong Chen MD and CR) independently evaluated studies for inclusion, and any disagreement was resolved by discussion. The criteria for inclusion were (1) proper randomization, (2) objectively diagnosed hemodynamically stable acute pulmonary embolism, (3) comparison of thrombolytic therapy and anticoagulant therapy for the initial treatment of pulmonary embolism, and (4) outcomes including death, pulmonary embolism recurrence, and bleeding. The criteria for exclusion were (1) $<$ 18 y of age, (2) pregnancy or lactation, and (3) objectively diagnosed massive acute pulmonary embolism.

Data Extraction

Two investigators (Hong Chen MD and CR) independently extracted data on the study design and quality and on the efficacy and safety outcomes during hospitalization or follow-up. In the event of discrepancy in the results obtained by the investigators concerning data extraction, the third investigator (Hong Chen MD PhD) helped in the final decision. Outcomes included (1) hemodynamically stable acute pulmonary embolism, (2) death, (3) pulmonary embolism recurrence, (4) major bleeding, (5) non-major bleeding, and (6) intracranial hemorrhage.

Assessment of Study Quality

We adopted the criteria for study quality outlined in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://www.cochrane.org/handbook, *accessed August 13, 2014*) in the evaluation of studies included in the present meta-analysis. These criteria include (1) proper random sequence generation, (2) proper concealment of the allocation sequence, (3) blinding of the patient and the investigator assessing clinical outcomes to treatment allocation, and (4) completeness of follow-up. Two investigators (Hong Chen MD and CR) independently evaluated study quality, and any disagreements were resolved by discussion.

Outcomes

The primary efficacy outcome was a composite of recurrent pulmonary embolism or death. Secondary outcomes were the individual components of the primary outcome, and safety outcomes were major bleeding, non-major bleeding, and intracranial hemorrhage.

Statistical Analysis

We used a meta-analysis of all randomized trials comparing thrombolytic therapy and anticoagulant therapy in subjects with moderate pulmonary embolism by curative effect and safety index. Relative risks were combined using the Cochrane RevMan 5.2 software. We assessed the heterogeneity between studies with the Cochran Q test and took $P < .05$ as the threshold of statistical significance for heterogeneity and for calculating the effect of the odds ratio (OR) and 95% CI. After clarifying the study effect of heterogeneity, we used a fixed-effects model based on the Mantel-Haenszel method[5] for combining results from the individual trials. Potential publication bias was evaluated using the funnel plot approach.

Results

Studies Included

Figure 1 shows the study selection process. Sixteen RCTs comparing thrombolysis and anticoagulant therapy for sub-

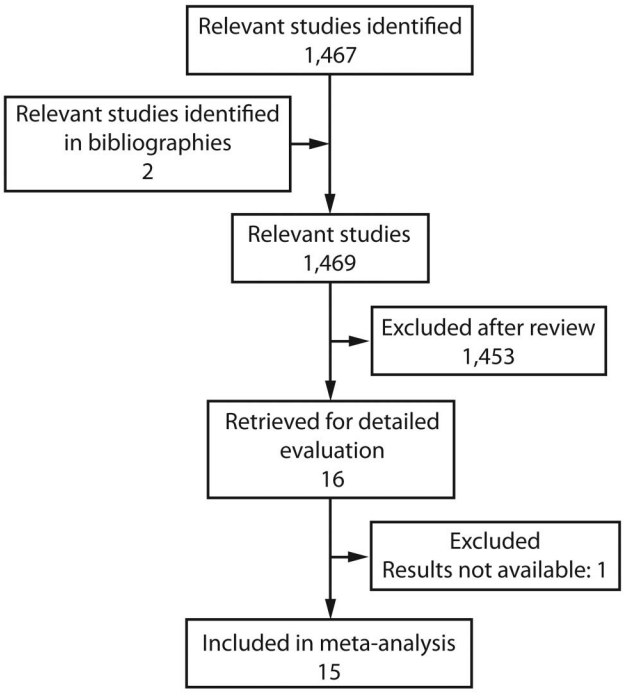

Fig. 1. Study flow chart.

jects with moderate pulmonary embolism were identified. Nine of the 16 trials were published in a foreign language and enrolled ~1,708 subjects[7-15]: one of them was excluded from this analysis because it was only a design and its results had not yet been published,[15] and the other 8 trials involved 708 subjects (347 subjects treated with thrombolysis and 361 subjects treated with heparin). Seven of the 16 trials were Chinese documents involving 539 subjects with moderate pulmonary embolism[16-22]: 270 subjects treated with thrombolysis and 269 subjects treated with anticoagulant therapy. The designs of the studies included in the meta-analysis are summarized in Table 1.

Study Quality

Table 2 shows the methodological quality of randomized studies of thrombolysis for moderate pulmonary embolism. Randomized treatment allocation sequences were generated with random number tables or programs in 5 studies.[11-14,20,] Information about proper concealment of the treatment allocation was provided in one trial.[10] Both subjects and investigators were blinded to treatment allocation in 5 trials.[7,8,11-13] The number of subjects lost to follow-up was reported in 3 of the 15 trials.[14,16,22]

Efficacy Outcomes

Data on the primary outcome of recurrent pulmonary embolism or death are presented in Figure 2, and individual components of this outcome are presented in Table 3. Nine of the 15 studies showed a reduction in recurrent pulmonary embolism or death with thrombolysis compared with anticoagulant therapy.[10,12-14,16,18-20,22] The pooled estimate from all of the trials revealed a statistically significant reduction in recurrent pulmonary embolism or death (1.94% vs 5.87%, OR 0.37, 95% CI 0.21–0.66), with no statistical evidence of heterogeneity among the studies ($P = .49$). Similar estimates of treatment effect were obtained for death (1.46% vs 3.81%, OR 0.45, 95% CI 0.23–0.86) and recurrent pulmonary embolism (0.81% vs 3.65%, OR 0.32, 95% CI 0.14–0.70).

Safety Outcomes

Pooled data for safety outcomes are presented in Table 4. Eight of the 15 randomized trials suggested an increase in major bleeding for thrombolytic therapy compared with anticoagulant therapy.[8-10,12,13,16,21,22] Nine of the randomized trials showed an increase in non-major bleeding with thrombolysis compared with heparin treatment.[7,9,12,13,17,19-21,22] The pooled data revealed a nonstatistically significant increase in major bleeding (3.57% vs 2.67%, OR 1.34, 95% CI 0.70–2.58) but a statistically significant increase in non-major bleeding (12.78% vs 3.65%, OR 4.12, 95% CI 2.37–7.17).

Subgroup Analyses

Table 5 provides a subgroup analysis comparing foreign and Chinese subjects. Compared with heparin treatment, thrombolytic therapy was associated with a significant reduction in recurrent pulmonary embolism or death in the 8 studies with 708 foreign subjects with moderate pulmonary embolism (3.46% vs 7.76%, OR 0.45, 95% CI 0.23–0.86) and in the 7 trials with 539 Chinese subjects (0.00% vs 3.72%, OR 0.18, 95% CI 0.05–0.73), with no statistical evidence of heterogeneity ($P = .12$). Similar estimates of treatment safety were obtained for major bleeding in foreign subjects (3.46% vs 2.77%, OR 1.19, 95% CI 0.51–2.79) and Chinese subjects (3.70% vs 2.23%, OR 1.59, 95% CI 0.57–4.45), with no statistical evidence of heterogeneity ($P = .67$).

Sensitive Analyses

Deletion of individual trials did not significantly change the primary outcome. Because this meta-analysis included randomized trials with small samples, most of scatter distributed at the bottom of the funnel plot (Fig. 3). The funnel plot of effect size versus study precision was comparatively symmetrical, with a similar number of studies on either side of the summary treatment effect for recurrent pulmonary embolism or death. This is consistent with a lack of major publication bias.

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Table 1. Design of Studies Included in the Meta-Analysis

Reference	PE Severity	Eligibility	Treatment	*n*	PE Assessment	Follow-up
Levine et al[7]	Moderate	Acute PE symptoms ≤ 14 d	rt-PA, 2 min	33	AGF, LS	10 d
			Heparin	25		
PIOPED[8]	Moderate	Acute PE symptoms ≤ 7 d	rt-PA, 40–90 min	9	AGF, LS	7 d
			Heparin	4		
PAIMS[9]	Moderate	Acute PE symptoms ≤ 10 d	rt-PA, 2 h	20	AGF	30 d
			Heparin	16		
Goldhaber et al[10]	Moderate	Acute PE symptoms ≤ 14 d	rt-PA, 2 h	46	AGF, LS	In-hospital or 14 d
			Heparin	55		
Konstantinides et al[11]	Moderate	Acute PE symptoms ≤ 4 d	rt-PA, 2 h	118	AGF, LS, spiral CT	In-hospital or 30 d
			Heparin	138		
Lu et al[16]	Moderate	Acute PE symptoms ≤ 14 d	Urokinase, 2 h	51	CT pulmonary angiography	12 mo
			Heparin	55		
Becattini et al[12]	Moderate	Acute PE symptoms ≤ 10 d	Tenecteplase bolus, 6 h	23	AGF, LS, spiral CT	7 d
			Heparin	28		
Fasullo et al[13]	Moderate	Acute PE symptoms ≤ 6 h	Alteplase, 2 h	37	Spiral CT	6 mo
			Heparin	35		
Wei and Sun[17]	Moderate	Acute PE symptoms ≤ 14 d	rt-PA, 2 h	28	CT pulmonary angiography	14 d
			Heparin	26		
Ou[18]	Moderate	Acute PE symptoms ≤ 14 d	Urokinase, 2 h	54	CT pulmonary angiography	7 d
			Heparin	54		
Sun[19]	Moderate	Acute PE symptoms	Urokinase, 2 h, 2 d	46	CT pulmonary angiography	30 d
			Heparin	46		
Wu et al[20]	Moderate	Acute PE symptoms	Urokinase, 2 h	35	CT pulmonary angiography	> 6 mo
			Heparin	35		
Zhang et al[21]	Moderate	Acute PE symptoms ≤ 14 d	rt-PA, 2 h	26	CT pulmonary angiography	14 d
			Heparin	29		
MOPETT[14]	Moderate	Acute PE symptoms ≤ 10 d	Weight ≥ 50 kg, 50 mg rt-PA Weight ≤ 50 kg, 0.5 mg rt-PA/kg	61	CT pulmonary angiography	28 mo
			Heparin	60		
Liu et al[22]	Moderate	Acute PE symptoms	rt-PA, 2 h	30	CT pulmonary angiography	6 mo
			Heparin	24		

PE = pulmonary embolism
PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis
PAIMS = Plasminogen Activator Italian Multicenter Study
MOPETT = Moderate Pulmonary Embolism Treated with Thrombolysis
rt-PA = recombinant tissue-type plasminogen activator
AGF = angiography
LS = lung scan
CT = computed tomography

Discussion

This meta-analysis of currently available RCTs showed some statistically significant benefits from thrombolytic therapy compared with anticoagulant therapy for the initial treatment of patients with moderate pulmonary embolism. Thrombolysis can reduce mortality or recurrence rate in patients with moderate pulmo-

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Table 2. Methodological Quality of Randomized Studies of Thrombolysis in Pulmonary Embolism

Reference	Random Sequence Generation	Allocation Concealment	Double-Blind	Loss to Follow-Up	Baseline Differences
Levine et al[7]	Unclear	Not stated	Yes	No	No
PIOPED[8]	Unclear	Not stated	Yes	No	No
PAIMS[9]	Unclear	Not stated	No	Not stated	Yes
Goldhaber et al[10]	Unclear	Yes	No	No	No
Konstantinides et al[11]	Clear	Not stated	Yes	Not stated	No
Lu et al[16]	Unclear	Not stated	No	Yes	No
Becattini et al[12]	Clear	Not stated	Yes	Not stated	No
Fasullo et al[13]	Clear	Not stated	Yes	Not stated	No
Wei and Sun,[17]	Unclear	Not stated	No	No	No
Ou[18]	Unclear	Not stated	No	No	No
Sun[19]	Unclear	Not stated	No	No	No
Wu et al[20]	Clear	Not stated	No	Not stated	No
Zhang et al[21]	Unclear	Not stated	No	No	No
MOPETT[14]	Clear	Not stated	No	Yes	No
Liu et al[22]	Unclear	Not stated	No	Yes	No

PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis
PAIMS = Plasminogen Activator Italian Multicenter Study
MOPETT = Moderate Pulmonary Embolism Treated with Thrombolysis

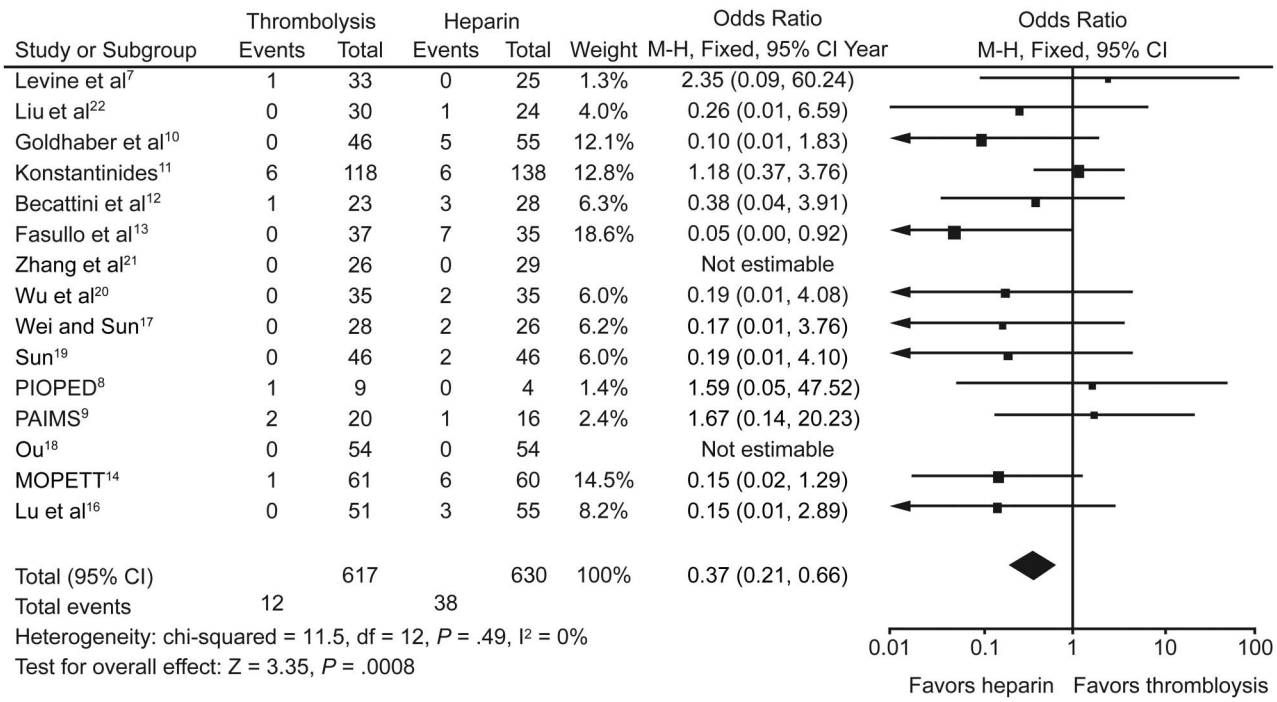

Fig. 2. The primary outcome of recurrent pulmonary embolism or death for thrombolysis versus anticoagulant therapy for the initial treatment of moderate pulmonary embolism. PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; PAIMS = Plasminogen Activator Italian Multicenter Study; MOPETT = Moderate Pulmonary Embolism Treated with Thrombolysis.

nary embolism. Compared with anticoagulation, thrombolytic therapy was associated with a significant reduction in recurrent pulmonary embolism or death in trials that also enrolled both foreign subjects with moderate pulmonary embolism and Chinese subjects. Nine studies[10,12-14,16,18-20,22] showed a lower mortality or recurrence rate with thrombolysis compared with anticoagulation for the initial treatment of moderate pulmonary embolism. Compared with anticoagulation, thrombolytic therapy was associated with a significant

Table 3. Data on Primary Outcome of Recurrent Pulmonary Embolism or Death

Outcome	Thrombolysis, *n/N* (%)	Heparin, *n/N* (%)	OR (95% CI)	*P* (Heterogeneity)
Recurrent pulmonary embolism or death	12/617 (1.94)	37/630 (5.87)	0.37 (0.21–0.66)	.49
Death	9/617 (1.46)	24/630 (3.81)	0.45 (0.23–0.86)	.75
Recurrent pulmonary embolism	5/617 (0.81)	23/630 (3.65)	0.32 (0.14–0.70)	.50

OR = odds ratio.

Table 4. Pooled Data for Safety Outcomes of Thrombolysis Versus Heparin Treatment

Outcome	Thrombolysis, *n/N* (%)	Heparin, *n/N* (%)	OR (95% CI)	*P* (Heterogeneity)
Major bleeding	22/617 (3.57)	16/630 (2.67)	1.34 (0.70–2.58)	.85
Non-major bleeding	69/540 (12.78)	20/548 (3.65)	4.12 (2.37–7.17)	.37
Bleeding	70/564 (12.41)	35/578 (6.06)	2.14 (1.36–3.36)	.21

Table 5. Subgroup Analysis of Foreign and Chinese Subjects

Outcome	Foreign Subjects			Chinese Subjects			*P* (Heterogeneity)
	Thrombolysis, *n/N* (%)	Heparin, *n/N* (%)	OR (95% CI)	Thrombolysis, *n/N* (%)	Heparin, *n/N* (%)	OR (95% CI)	
Recurrent pulmonary embolism or death	12/347 (3.46)	28/361 (7.76)	0.45 (0.23–0.86)	0/270 (0.00)	10/269 (3.72)	0.18 (0.05–0.73)	.12
Death	9/347 (2.59)	16/361 (4.43)	0.58 (0.27–1.24)	0/270 (0.00)	8/269 (2.97)	0.22 (0.05–0.88)	.11
Recurrent pulmonary embolism	5/347 (1.44)	19/361 (5.26)	0.35 (0.15–0.82)	0/270 (0.00)	4/269 (1.49)	0.19 (0.02–1.66)	.57
Major bleeding	12/347 (3.46)	10/361 (2.77)	1.19 (0.51–2.79)	10/270 (3.70)	6/269 (2.23)	1.59 (0.57–4.45)	.67

increase in non-major bleeding but a nonsignificant increase in major bleeding.

Compared with previous meta-analyses, this study has provided conflicting conclusions about the benefits of thrombolysis in patients with moderate pulmonary embolism. A recent meta-analysis,[6] which included only 5 randomized trials[7-11] and involved 464 subjects, reported no significantly decreased mortality or recurrent pulmonary embolism, whereas we showed a significant benefit of thrombolysis compared with anticoagulation for the initial treatment of moderate pulmonary embolism. Our study included 15 trials involving 1,247 subjects and could lead to more valid results for the initial treatment of moderate pulmonary embolism. The subgroup analysis, which included 8 foreign studies involving 708 subjects, also showed that thrombolysis resulted in a significant reduction in pulmonary embolism recurrence or death compared with heparin treatment. The Pulmonary Embolism Thrombolysis (PEITHO) trial[15] is a prospective, multi-center, international, randomized, double-blind comparison of tenecteplase versus placebo in subjects with moderate pulmonary embolism and is expected to enroll ~1,000 subjects, to determine the benefits versus risks of thrombolysis in moderate pulmonary embolism, and to answer a query on the management of this patient population; the

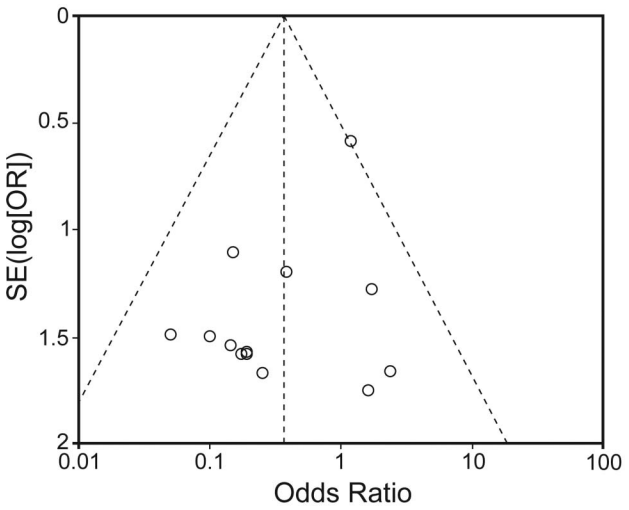

Fig. 3. Funnel plot of effect size versus study precision of recurrent pulmonary embolism or death. OR = odds ratio.

authenticity of the result of this meta-analysis can be further defined. Geibel et al[23] pointed out that women with submassive pulmonary embolism might benefit less from thrombolytic treatment in terms of survival and pulmonary embolism recurrence and that they could be exposed to a higher bleeding risk compared with men. Compared with previous meta-analyses, this meta-analysis included more randomized trials, and the number of men compared with women in the Chinese studies included was larger. Perhaps the greater reduction in mortality and pulmonary embolism recurrence with thrombolysis was due to the larger number of male subjects. However, the ratio of male to female subjects in the foreign studies was close to 1:1, which supports the conclusion of this meta-analysis that thrombolytic therapy can reduce mortality and pulmonary embolism recurrence rate. Because the study by Geibel et al[23] is not an RCT, it is necessary to use large RCTs to determine whether there are differences between males and females regarding the benefits and risks of thrombolytic therapy for moderate pulmonary embolism.

We conclude that thrombolysis can improve clinical outcome and is worth putting into clinical practice. Because the total hemorrhage rate of thrombolysis was 2 times that of anticoagulant therapy in subjects with moderate pulmonary embolism, the clinical application of thrombolytic therapy is still limited. Based on the conditions and weights of patients, reducing the dose of thrombolytic drugs can decrease the risk of major bleeding[8,14]; thus, we look forward to more clinical studies to determine the safe dose of thrombolysis for moderate pulmonary embolism. Of course, because of deterioration during anticoagulant therapy, upgraded treatment such as thrombolysis was selected, which can improve symptoms quickly, reduce pulmonary artery pressure, and improve right ventricle dysfunction.[11,17] In addition, thrombolysis does cause a decline in the event-free survival rate after a 1-y follow-up compared with anticoagulation.[16] The efficacy of thrombolysis could be confirmed by expanding the limited follow-up time.

This study has several potential limitations. First, in every study included, the number of subjects and the number of outcome events are low, so this meta-analysis has a limited statistical power. However, compared with previous meta-analyses, ours included more studies. Second, our meta-analysis included 7 Chinese studies. Although they clarified the consistent research group and control group at baseline, most of the literature did not show random distribution. Due to ethnic differences, we performed a subgroup analysis of foreign and Chinese subjects. Finally, the trials did not limit follow-up time. However, this does not preclude pooling of the results because it is only within the same studies that subjects are directly compared with each other. Because the trials that were included in this meta-analysis did not limit the type or dosage of thrombolytic drugs, this may be the major bias in this analysis. However, one previous meta-analysis[24] concluded that different thrombolytic drugs share similar efficacy and safety.

Conclusions

Both mortality and pulmonary embolism recurrence are decreased by thrombolysis compared with heparin treatment in patients with moderate pulmonary embolism. Thrombolysis is worth putting into clinical practice. However, this study and the previous meta-analyses have reached conflicting conclusions regarding the efficacy of thrombolysis. Compared with heparin treatment, thrombolytic therapy increases the risk of non-major bleeding, but not major bleeding. Further evaluation of the efficacy and safety of thrombolysis for the treatment of moderate pulmonary embolism appears to be warranted.

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REFERENCES

1. Aujesky D, Jimenez D, Mor MK, Geng M, Fine MJ, Ibrahim SA. Weekend versus weekday admission and mortality after acute pulmonary embolism. Circulation 2009;119(7):962-968.
2. Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117(13):1711-1716.
3. Ramakrishnan N. Thrombolysis is not warranted in submassive pulmonary embolism: a systematic review and meta-analysis. Crit Care Resusc 2007;9(4):357-363.
4. Worster A, Smith C, Silver S, Brown MD. Evidence-based emergency medicine/critically appraised topic. Thrombolytic therapy for submassive pulmonary embolism? Ann Emerg Med 2007;50(1):78-84.
5. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004; 110(6):744-749.
6. Tardy B, Venet C, Zeni F, Coudrot M, Guyomarc'h S, Mismetti P. Short term effect of recombinant tissue plasminogen activator in patients with hemodynamically stable acute pulmonary embolism: results of a meta-analysis involving 464 patients. Thromb Res 2009; 124(6):672-677.
7. Levine M, Hirsh J, Weitz J, Cruickshank M, Neemeh J, Turpie AG, Gent M. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with pulmonary embolism. Chest 1990;98(6):1473-1479.
8. PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study. Chest 1990;97(3):528-533.
9. Dalla-Volta S, Palla A, Santolicandro A, Giuntini C, Pengo V, Visioli O, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen Activator Italian Multicenter Study 2. J Am Coll Cardiol 1992;20(3): 520-526.
10. Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism:

RESPIRATORY CARE Paper in Press. Published on September 30, 2014 as DOI: 10.4187/respcare.03197

randomized trial assessing right ventricular function and pulmonary perfusion. Lancet 1993;341(8844):507-511.
11. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, 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(15):1143-1150.
12. Becattini C, Agnelli G, Salvi A, Grifoni S, Pancaldi LG, Enea I, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res 2010; 125(3):e82–e86.
13. Fasullo S, Scalzo S, Maringhini G, Ganci F, Cannizzaro S, Basile I, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. Am J Med Sci 2011;341(1):33-39.
14. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M, "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111(2):273-277.
15. Steering Committee. Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 2012;163(1): 33.e1-38.e1.
16. Lu WH, Tang ZZ, Ma Y, Yu ZH. Long term prognosis of thrombolytic therapy with urokinase and/or anticoagulant in submassive pulmonary embolism. Clin J Med Offic 2008;36(3):340-342.
17. Wei L, Sun FC. Curative effect of thrombolysis and anticoagulant therapy on submassive pulmonary embolism patients. Int J Respir 2012;32(19):1471-1473.
18. Ou YQ. Analysis of therapeutic effect of urokinase combined with sequential anti-coagulation in submassive pulmonary embolism. J Hainan Med Univ 2012;18(7):897-898.
19. Sun RQ. Curative effect of urokinase combined with low-molecular-weight heparin, warfarin in submassive pulmonary embolism. Strait Pharm J 2012;24(5):130-131.
20. Wu TX, Lin GS, Chen GH, Chen LQ. Curative effect of thrombolysis combined with sequential anti-coagulation in submassive pulmonary embolism. J Clin Intern Med 2012;28(12):835-836.
21. Zhang XL, Jiang SH, Jiang LN, Shan FL, Li Z, Qin MH. Clinical observation of small doses of rt-PA thrombolysis for 26 cases of elderly patients with acute submassive pulmonary embolism. Shandong Med J 2012;52(3):69-70.
22. Liu LH, Lu SJ, Liu Z. Curative effect of thrombolysis and anticoagulant therapy for patients with submassive pulmonary embolism. Chongqing Med 2013;42(11):1288-1290.
23. Geibel A, Olschewski M, Zehender M, Wilsch M, Odening K, Heinrich F, et al. Possible gender-related differences in the risk-to-benefit ratio of thrombolysis for acute submassive pulmonary embolism. Am J Cardiol 2007;99(1):103-107.
24. Qin ZQ, Wang C. Comparison of different thrombolytics in treatment of pulmonary thromboembolism: a meta-analysis. Sect Respir Sys Foreign Med Sci 2005;25(1):1-4.