

Effectiveness of Thrombolysis in Patients with Intermediate-Risk Pulmonary Embolism: Influence on Length of Hospital Stay

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ABSTRACT

Introduction: The effects of thrombolysis on the clinical outcome of patients with intermediate-risk pulmonary embolism (PE) are still under debate. The effect of thrombolysis on the length of stay (LOS) in hospital is unknown. The aim of this study was to identify factors associated with LOS and to investigate whether LOS is suitable to assess effectiveness of thrombolysis in patients with intermediate-risk PE. **Methods:** Data were reviewed from December 2005 until October 2009. The LOS in the intensive care unit (ICU) was expressed in hours, and total LOS was recorded in days. Total LOS was not noted in case of preterm withdrawal of therapy or death. **Results:** Of a total of 202 patients, 84 received alteplase plus heparin and 118 patients were treated with anticoagulants alone. Total median LOS

was significantly shorter (10 vs. 12 days) in the alteplase group ($P=0.005$), while there was no difference in the LOS in the ICU. Age above 65 years ($P=0.036$) and comorbidity ($P<0.001$) were independent predictors for a prolonged hospital stay, whereas thrombolysis independently predicted a shorter total LOS in multivariate analysis ($P=0.001$). Thrombolysis has shown to be able to independently predict home discharge ($P=0.029$). **Conclusion:** LOS is influenced by patient-related factors such as age and comorbidity. Thrombolysis may lead to a reduction of total median LOS for patients with intermediate-risk PE, possibly indicating that it is more effective than anticoagulant therapy alone in this group of patients.

Keywords: effectiveness of therapy; intermediate-risk pulmonary embolism; length of hospital stay; thrombolysis

INTRODUCTION

Thrombolysis is the standard treatment for patients with massive pulmonary embolism (PE) leading to hemodynamic instability and cardiogenic shock.¹ In contrast, considering the potential side effects of therapy and the

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natural course of the disease, thrombolysis is not recommended in hemodynamically stable patients without any evidence of right heart failure.² The effects of thrombolytic treatment on the clinical outcome of normotensive patients with signs of right ventricular dysfunction (RVD) and/or myocardial injury (the so-called intermediate-risk group) are still debated and difficult to assess.² Only very few trials have been conducted in hemodynamically stable patients designed to address clinical endpoints.³ Konstantinidis et al. were able to show that thrombolysis in normotensive patients with PE and evidence of RVD may prevent further clinical deterioration requiring an escalation of treatment such as catecholamine infusion, mechanical ventilation, or secondary thrombolysis; however, they found no effect on the in-hospital mortality.⁴ The authors conclude that the indication for thrombolysis should be extended to hemodynamically stable patients with manifestation of RVD. However, thrombolytic therapy carries a significant risk of bleeding, especially when predisposing conditions and comorbidity exist.^{1,5} Therefore, some authors do not support the routine use of thrombolysis in normotensive patients with PE and signs of RVD.⁶⁻⁸

Although influenced by many factors, the length of hospitalization might be an appropriate indicator for the effectiveness of thrombolytic therapy in patients with PE, since both potential clinical benefits as well as complications will affect the length of stay (LOS). The effect of thrombolysis on LOS of patients with PE is unknown. We sought to identify factors associated with LOS in patients with intermediate-risk PE and to investigate whether LOS is suitable to assess effectiveness of thrombolytic treatment in this group of patients.

MATERIALS AND METHODS

In this single-center study at a large, tertiary, academic teaching hospital, data of patients referred to the intensive care unit (ICU) because of PE and signs of RVD and/or myocardial injury were retrospectively reviewed from December 2005 until October 2009. The study follows currently accepted ethical guidelines. All patients had compulsory health insurance coverage. Diagnosis was confirmed by multidetector computed tomography (CT) angiography. We considered patients hemodynamically stable with a systolic arterial pressure more than 90 mmHg according to earlier studies.^{4,9} Initial anticoagulant therapy consisted of both fractionated and unfractionated heparin, and was started immediately after diagnosis in all cases. All patients on oral anticoagulants were set on a vitamin K antagonist with an international normalized ratio (INR) of >2.0 at time of discharge from the hospital. Thrombolysis was performed with 100 mg of alteplase as described before.⁴ Contraindications to thrombolysis were defined according to current guidelines.² The LOS was calculated using the support of the hospital's electronic data processing system (ORBIS OpenMed, Agfa Health Care, Bonn, Germany) expressing the LOS on the ICU in hours rounded up to the nearest half hour. Total LOS was expressed in days between admission and discharge, not subdivided by the hours of the day. In case of readmission to the ICU, hours were added. LOS was not noted in case of preterm withdrawal of therapy or death during hospitalization (in case of death after discharge from ICU, LOS on ICU was registered).

RVD was diagnosed by echocardiography on the day of admission to the ICU and assessed according to current guidelines.² In addition, biomarkers like troponin I (TNI) and N-terminal-

pro brain natriuretic peptide (NT-proBNP) were used for risk stratification. TNI levels were determined immediately after admission. NT-proBNP measurements were considered when blood was drawn within 48 hours after time of diagnosis in regard of the longer pharmacological stability of NT-proBNP in contrast to BNP levels.^{10,11} NT-proBNP levels >125 pg/mL were considered elevated for patients younger than 75 years and >450 pg/mL for those older than 75 years.¹² TNI levels >0.09 ng/mL were regarded elevated for all age groups.¹³

Escalation of treatment (readmission to the ICU, rescue thrombolysis, or resuscitation) and clinical deterioration such as recurrent PE or ischemic stroke were considered as clinical worsening according to an earlier study.⁴ Major bleeding was defined as lethal bleeding, intracerebral hemorrhage confirmed by CT or magnetic resonance imaging, or a drop in the hemoglobin concentration by at least 4 g/dL.⁴ All other bleeding complications were considered to be minor. Asthma, chronic obstructive pulmonary disease, emphysema, lung fibrosis, sarcoidosis, lung or pleural cancer were considered as concomitant lung diseases. Comorbidity was defined as concomitant lung disease, left ventricular ejection fraction <40%, renal insufficiency, and active cancer.

Statistical analysis was performed with SPSS software for Windows version 12.0 (SPSS, Chicago, IL, USA). Variables are shown as mean \pm 1 standard deviation or as medians with range. The Student's *t* test was used for the comparison of continuous variables and the χ^2 test for the comparison of nominal variables. Multivariate analysis of variance (MANOVA) was performed to investigate the individual influence of thrombolysis, age and comorbidity on the LOS and other variables, and to detect potential confounding effects among the covariates. A probability value of less than 0.05

was considered statistically significant, and all reported *P* values are two-tailed.

RESULTS

A total of 202 patients with intermediate-risk PE were admitted to the ICU. In all, 84 patients received thrombolytic therapy and 118 patients were treated with anticoagulants alone, 88 in the absence of relative or absolute contraindications for thrombolysis. There was no difference in gender in both groups. Patients who were treated with alteplase in addition to heparin were significantly younger ($P<0.001$) and had less comorbidity ($P<0.001$) than those treated with anticoagulants alone. Clinical worsening was less common in patients who received thrombolysis ($P=0.005$), while there was a significantly higher incidence of minor bleeding in the alteplase group ($P=0.003$). In-hospital mortality was significantly ($P=0.025$) lower in patients receiving thrombolytic treatment. Patients treated with alteplase in addition to heparin were more frequently discharged home without further treatment than patients receiving anticoagulants alone ($P=0.010$). Out of 24 patients who could not be discharged home, 22 were transferred to other hospitals; two patients were referred to rehabilitation centers. Total median LOS was significantly shorter (10 vs. 12 days) in patients who received thrombolytic therapy ($P=0.005$), while there was no difference in the LOS in the ICU in both groups (Table 1).

MANOVA (Table 2) revealed age above 65 years ($P=0.036$) and concomitant diseases ($P<0.001$) to be independently associated with a longer total LOS, while only comorbidity ($P<0.001$) predicted a prolonged stay in the ICU. In contrast, thrombolysis independently predicted a shorter total LOS in multivariate analysis ($P=0.001$). The influence of thrombolysis, age, and comorbidity on clinical worsening did not

Table 1. Clinical characteristics* of patients with and without thrombolytic therapy.

Characteristic	All	Thrombolysis	No thrombolysis	P value
Total	202	84	118	
Male	96 (47.5)	44 (52.4)	52 (44.1)	0.279
Female	106 (52.5)	40 (47.6)	66 (55.9)	0.279
Age (mean±SD)	62.0±18.0	57.9±18.0	67.4±15.3	<0.001
Clinical worsening	15 (7.4)	1 (1.2)	14 (11.9)	0.005
Mortality	12 (5.9)	1 (1.2)	11 (9.3)	0.025
Not discharged home	24 (11.9)	5 (6.0)	19 (16.1)	0.010
Length of stay:				
ICU in hours (median, range)	22, 3-125.5	23, 7-27	21, 3-125.5	0.665
Total in days (median, range)	11, 6-75	10, 6-75	12, 6-46	0.005
Contraindications to thrombolysis:				
Absolute	10 (5.0)	0	10 (8.5)	
Relative	23 (11.4)	3 (3.6)	20 (16.9)	
Bleeding:				
Minor	5 (2.5)	5 (6.0)	0	0.003
Major	2 (1.0)	2 (2.4)	0	0.063
Comorbidity (left ventricular ejection fraction <40%, concomitant lung disease, renal insufficiency or active cancer)	41 (20.3)	9 (10.7)	32 (27.1)	<0.001

*When not stated otherwise, values are given as *n* and % of total. ICU=intensive care unit.

Table 2. Multivariate analysis of variance (MANOVA) on individual influence of thrombolytic therapy, age, and comorbidity on the length of hospital stay and other variables.

Dependent variable	Thrombolysis		Age >65 years		Comorbidity	
	F value	P value	F value	P value	F value	P value
Length of hospital stay in ICU	2.018	0.157	0.129	0.720	13.833	<0.001
Total length of hospital stay	10.426	0.001	4.479	0.036	31.072	<0.001
Clinical worsening	2.658	0.105	0.562	0.454	0.066	0.797
Mortality	5.103	0.025	0.835	0.362	21.520	<0.001
Not discharged home	4.829	0.029	4.879	0.028	6.131	0.014
Minor bleeding	7.488	0.007	4.903	0.028	0.011	0.995
Major bleeding	1.421	0.235	0.768	0.382	0.247	0.620

ICU=intensive care unit.

reach a significant level in multivariate analysis. Alteplase therapy was associated with a greater incidence of minor bleedings ($P=0.007$), while there was no statistically significant association with major bleeding complications ($P=0.235$). Older age has turned out to be an individual

predictor of minor bleedings ($P=0.028$). Thrombolysis was associated with a lower in-hospital mortality rate in multivariate analysis ($P=0.025$), whereas comorbidity independently predicted a higher death rate during the hospital stay ($P<0.001$). Thrombolysis and younger age

were shown to predict home discharge without further rehabilitation in multivariate analysis ($P=0.029$ and 0.028 , respectively). In contrast, comorbidity was an individual risk factor raising the likelihood of not being discharged home without further treatment ($P=0.014$).

DISCUSSION

In contrast to the largest, randomized, controlled trial in patients with intermediate-risk PE⁴ we were able to demonstrate that thrombolysis is significantly associated with a reduction of the in-hospital mortality in univariate and multivariate analysis. The higher death rate in patients not receiving thrombolysis observed in our study might be due to the fact that all our patients had signs of RVD documented by echocardiography or elevated biomarkers, while only 30% of the participants in the trial mentioned above met these criteria.⁶ Therefore, one might conclude that the patients described in our study were more severely ill and consequently benefited to a greater extent from thrombolytic treatment.

As previously described⁴ and confirmed by our observation, the mortality rate in intermediate-risk PE is generally low. Thus, the effectiveness of thrombolysis for the majority of patients with submassive PE remains difficult to assess. We therefore investigated the LOS as a potential indicator for the effectiveness of treatment. Compared with another report dealing with LOS in PE,¹⁴ economic factors did not have any influence in our study as all patients had compulsory health insurance coverage. Although conducted as a single-center study, patient characteristics are similar to earlier multicenter investigations^{4,15} and therefore, data seem to be generalizable.

Thrombolysis does not have any effect on LOS on the ICU, but it is disputable if

this parameter is appropriate in indicating effectiveness of therapy. According to our local standards, all patients with intermediate-risk PE were transferred to the ICU for observation or possible thrombolysis. Thus, all our patients were normotensive but had evidence of RVD and/or myocardial injury. In this respect, both groups were homogenous and well comparable. Nevertheless, we cannot exclude that patients were transferred to the ICU because they suffered from concurrent diseases in addition to PE and therefore we are not able to safely rule out a bias. Moreover, compared to treatment with anticoagulants alone, it is likely that patients receiving thrombolytic agents require a prolonged observation on the ICU considering potential side effects of therapy and the need of prompt reaction when bleeding complications occur. Pooled data analysis³ revealed a 9% to 22% risk for major and minor bleeding; thus, an alert follow-up for patients treated with thrombolytic agents is certainly justified. Bleeding complications might be underestimated in our observation as minor bleedings were possibly omitted in the medical records or thrombolysis might have been restricted to younger and healthier patients. However, we were able to show that minor bleedings were clearly associated with thrombolysis. Therefore, therapy due to bleeding complications might partly explain the longer LOS of patients treated with alteplase on the ICU, but it seems not to be justified to infer a relevant disadvantage of therapy from that fact since the difference in LOS is statistically not significant.

In contrast to a longer LOS on the ICU, we were able to demonstrate that patients receiving thrombolysis in addition to heparin could be discharged from hospital significantly earlier. One might argue that the difference of 2 days (10 vs. 12 days) is marginal. However, the shorter total LOS in the alteplase group seems

to be underestimated, because significantly more patients receiving thrombolytic treatment could be discharged directly to their home without requiring further treatment. Most patients referred to other institutions were transferred to hospitals rather than to rehabilitation centers; thus, we believe that the total LOS might rather be underestimated than prolonged, because the waiting time for such a referral is generally short.

As patients receiving thrombolysis were significantly younger and had less concomitant diseases than those treated with anticoagulants alone, we had to face the potential confounding effects of age and comorbidity. In order to further evaluate these potential confounders, we performed a multivariate statistical analysis. In a MANOVA model, older age and comorbidity independently predict a longer median total LOS. Furthermore, age above 65 years and concomitant diseases were identified as individual risk factors preventing patients from being discharged home without further treatment. In case of comorbidity, the statistical power in predicting the LOS and place of discharge is strongest. However, the effect of comorbidity on total LOS might be overestimated. In contrast to a randomized trial, it is likely that in our observation multimorbid patients were excluded from receiving thrombolytic treatment; thus, potential benefits of thrombolysis might have been restricted to patients without comorbidity. This assumption is supported by the fact that in multivariate analysis, thrombolysis proved to be an independent predictor for a shorter total LOS and for home discharge without requiring further treatment.

The reasons for a shorter total LOS in patients treated with alteplase are speculative, particularly because we know from earlier studies that the hemodynamic benefits of thrombolysis over heparin appear to be confined to the first few days

of the hospital stay. At 1 week after thrombolytic treatment, for example, the changes in vascular obstruction¹⁶ and the reversal of RVD¹⁷ were no longer different between patients treated with alteplase in addition to heparin or anticoagulant therapy alone. As we can assume that all our patients were clinically stable for discharge, we speculate that thrombolysis may have stabilized the patients' clinical status more rapidly— independent from hemodynamic benefits— and that it may have contributed to a less complicated course of the disease, as already speculated in an earlier trial.⁴

CONCLUSION

To the best of our knowledge, this is the first report of the effects of thrombolytic therapy on the LOS in patients with intermediate-risk PE. LOS is influenced by patient-related factors such as age and comorbidity. Thrombolysis may lead to a reduction of total median LOS in patients with intermediate-risk PE. Postulating that a shorter total LOS results from a more effective therapy, we speculate that thrombolytic treatment may be more effective than anticoagulant therapy alone in normotensive patients with acute PE and signs of RVD, as defined by echocardiography or elevated biomarkers. Unfortunately, our study suffers from the intrinsic problem associated with every retrospective analysis of observational data, as multivariate analysis might not be able to fully eliminate a bias in the raw data. Large, randomized, controlled trials which are adequately powered to demonstrate that thrombolysis in addition to anticoagulant therapy improves survival need to be awaited in order to finally assess the effectiveness of thrombolysis in patients with submassive PE.^{6,18} Meanwhile, the reliance on less powerful observational studies might be justified.

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