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Comparison of side effects between thrombolytic and anticoagulation therapy in patients with pulmonary embolism

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Abstract

Purpose: The treatment of Pulmonary Embolism (PE) which is a life-threatening disease must be planned considering the risk-benefit relationship. In this study, patients with PE given thrombolytic therapy, low-molecular-weight heparin, and warfarin were monitored for 5 years to compare them in terms of hemorrhage side effects due to therapy.

Method: A total of 219 patients were included in the study. 50.2% (n=109) of the patient's were female and 49.8% (n=110) were male, (p=0.20). Clinical findings, radiologic and laboratory parameters, treatments and side effects were recorded. A total of 121 (55.25%) patients were given thrombolytic therapy (Group 1 n=121). Enoxaparin therapy was given to 205 patients (Group 2). During therapy maintenance, warfarin therapy was conducted for 159 patients (Group 3).

Results: Cerebral hemorrhage observed in 1 case (0.83%) in group 1, 2 case (0.98%) in group 2 and 1 cases (0.62%) in group 3 (p>0.05). Gastrointestinal system (GI) bleeding happened 2 cases (1.65%) in group 1 and 2 cases (0.98%) in group 2 (p>0.05). Minor bleeding was observed at similar rates due to the treatments. There was no fatality due to hemorrhage. There is no significant difference in terms of death, recurrence, residual chronic thrombus, and chronic PE in the follow-up for five years between the rt-PA group (group1) and non-rt-PA group (p>0.05).

Conclusion: According to our results; major hemorrhage was observed similarly in thrombolytic, enoxaparin, and warfarin therapy. Study results about the rate of cerebral hemorrhage related to thrombolytic therapy were low in contrast to the results reported in the literature before.

Keywords: Blood Coagulation Factors; Cardiovascular Diseases; Fibrinolytic Agents; Pulmonary Embolism; Respiratory System

1. Introduction

Thrombolysis is recommended for patients with acute massive pulmonary embolism having hemodynamic instability or cardiogenic shock in all guidelines about pulmonary embolism [1, 2]. Studies based on two large, multicenter registries reported that patients with right ventricular dysfunction due to pulmonary embolism had increased rates of in-hospital death, even in the absence of arterial hypotension or shock [2, 3]. So for the other patients not having hypotension but having a risk of mortality thrombolysis can be applied after a careful risk-benefit assessment [2].

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Although the benefit of thrombolysis in morbidity and mortality is mostly an accepted issue, the complications, especially intracerebral hemorrhage (ICH) are a major obstacle to adequate use. Several recent meta-analyses have appraised the risk of bleeding associated with thrombolysis in PE [4-6]. Unfortunately, the available data is not reliable enough which is some of them limited in size. There is significant heterogeneity in patient selection and treatment regimens.

After the results of numerous large studies had shown the effects and benefit of thrombolysis in ST-segment elevation myocard enfarctus (STEMI), thrombolysis in PE patients also started. ICH rates reported in STEMI were 0.94% [7]. while in PE 1% to 10% [6]. This marge is a lot for PE and it doesn't seem logical.

In this study, patients with PE who were given thrombolytic therapy, low-molecular-weight heparin (LMWH), and warfarin were evaluated and compared in terms of bleeding side effects especially ICH. The secondary outcome is to evaluate all cases in terms of death, recurrence, residual chronic thrombus, and chronic PE in the follow-up for five years.

2. Material and methods

2.1. Study Design and Participants

We performed a uni-center, retrospective, case-control trial design. The patients who were diagnosed with Pulmonary Embolism (PE) by Multislise (64 or 256 detectors) Thorax CT Angiography were included in the study. 219 patients' clinical findings, radiologic and laboratory parameters were recorded. The study was approved by the local ethics committee. Patients were classified by mortality risk according to the European Society of Cardiology (ESC)* criteria [2].

First patients were divided into two groups Group 1 is the PE patients that thrombolytic therapy was given, Group 2 is the PE patients that thrombolytic therapy was not given.

Then patients were divided into three groups according to the treatment agent used in PE therapy. Thrombolytic therapy was given to 121 patients (Group 1 n=121). Enoxaparin therapy was given to 205 patients (Group 2). During therapy maintenance, warfarin therapy was given to 159 patients (Group 3).

The patients diagnosed with acute PE treated by thrombolytic therapy within 14 days after the onset of symptoms. Recombinant tissue plasminogen activator (rt-PA) was administrated to the patients with high risk or moderate-high risk PE at a standard dose of 100 mg/2hours. All patients received low molecular weight heparin (LMWH)(enoxaparin sodium,) 12 hours after the thrombolytic therapy. The second group without thrombolytic therapy treatment was started with LMWH 1 mg/kg subcutaneously 2x1 and continued till the International Normalisation Ratio (INR) was up to 2,0 to 2,5 times the upper limit of the normal range in the patients receiving Coumadin. Treatment with oral anticoagulant or low-molecular-weight heparin was completed to 6 or 12 months according to the PE recurrence risk of each patient.

Patients were eligible for the study if they met all the following criteria: an age of 18 years or older, objectively confirmed acute pulmonary embolism diagnosed by multislise (64-256 detector) Thorax CT Angiography.

Patients were excluded: If they had been using any other drugs or have a concomitant disease that affects hemostasis. Patients' age, gender, and risk factors for PE were recorded. Genetic thrombosis risk analysis was performed in unprovoked cases.

All patients' systolic blood pressure, diastolic blood pressure, Wells score; serum D-Dimer, Troponin T, ProBNP, CK-mb, CK levels, and Echocardiographic findings were recorded. PE mortality risk classification was performed by evaluating echocardiographic (ECHO) findings (Philips iE33, İstanbul) and myocardial biomarkers in the blood.

2.2. Follow-up and Outcome Assessment

All cases' data were recorded using the hospital database, file archive, and telephone visit during the follow-up. Patients were followed up for 5 years and evaluated in terms of recurrent pulmonary embolism, residual chronic thrombus, chronic PE, and death.

Primary outcome assessment was defined as the presence of hemorrhage due to the treatment. There is a lot of hemorrhage description in the literature. We preferred the TIMI (Thrombolysis in Myocardial Infarction) study rules (8-10) for classifying the hemorrhage in this study:

Major: Any intracranial bleeding (excluding microhemorrhages 10 mm evident only on gradient-echo MRI), Clinically overt signs of hemorrhage associated with a drop in hemoglobin of 5 g/dL, Fatal bleeding (bleeding that directly results in death within 7 days)

Minor: Clinically overt (including imaging), resulting in hemoglobin drop of 3 to 5 g/dL

Requiring medical attention: Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above

Minimal: Any overt bleeding event that does not meet the criteria above.

LMWH was initiated 12 hours after rt-PA treatment. Bleeding in the first 48 hours after administration of rt-PA was considered to be associated with rt-PA. Most of the events were anticoagulated with warfarin while receiving enoxaparin. Subsequent bleeding after stopping enoxaparin was considered warfarin-associated hemorrhage.

The secondary endpoint of the study was a confirmed recurrence of pulmonary embolism, residual chronic thrombus, chronic PE which is defined by ESC criteria, and death within 30 days, in the first year and the fifth year.

Chronic PE was evaluated by CT pulmonary angiography at six months follow-up and lower extremity Doppler ultrasound was performed for chronic DVT diagnosis. The causes of recurrence were studied. In the first month of treatment, in the first year, and in the fifth year, death and the causes of death were recorded. The hospital records used for patients who died in our hospital and the national death notification system were used for other patients.

2.3. Statistics

Mean±standard deviation (SD) or median (interquartile range) for metric variables and frequency (percent) for categorical variables were used as descriptive statistics. The odds ratio with its 95% confidence interval was used to determine the effect of the independent factor on the dependent variable. The Chi-Square test was used to compare two independent groups for categorical variables, and Student's t-test or Mann-Whitney U test was used for metric variables. $p<0.05$ was considered as statistically significant.

3. Results

A total of 219 cases are included in the study. The median age of all cases was 68 (21-95). Eighty-one patients (37%) had high mortality risk, 62 (28.81%) had moderate-high risk and 76 (34.19%) had moderate-low and low risk.

Thrombolytic therapy was given to 121 patients (55.25%) (Group 1); 59 patients (26.94%) had high-risk mortality and 62 (28.31%) had moderate-high risk mortality.

In the thrombolytic receiving group 56 (46.29%) of the patients were male and 65 (53.71%) were female. In the non-thrombolytic group, 49 (50%) of the patients were male and 49 (50%) were female. Demographic data and general characteristics of treatment groups were shown in Table 1.

Baseline clinical characteristics of treatment groups and laboratory data were seen in Table 2. Systolic / diastolic blood pressure before treatment was significantly lower (p: 0.001) and right ventricular dysfunction and systolic pulmonary artery pressure were significantly higher in the thrombolytic group [Right ventricular dysfunction, OR6.25 95CI% (2.82-13.8) (p: 0.001)]. Wells's score and serum d-dimer levels were significantly high in the rt-PA receiving group compared with the non-rt-PA receiving group.

When all the cases were divided into three groups according to the treatment agent; Group1 whom thrombolytic therapy was given contained 121(55.25%) patients, Group 2 who received enoxaparin treatment was 205 patients. Group 3, Warfarin treatment was given to 159 patients.121 patients receiving rt-PA continued the treatment with enoxaparin. Of the 205 patients who received enoxaparin, 159 received warfarin whereas 46 patients continued using enoxaparin.

Table 1 Demographic data and general characteristics of treatment groups

	rt-PA+ (n = 121)	**rt-PA- (n = 98)**	**p**
Age, yrs Mean Median	 64.61±13.6 71 (30-95)	 66.46±16.1 68 (21-95)	 0.89
Gender, male	56 (46.28%)	49 (50%)	0.56
Obesity	2 (1.65%)	4 (4.08%)	1.000
Previous venous thromboembolism	3 (2.47%)	3 (3.06%)	0.670
Family history of VTE	2 (1.65%)	3 (3.06%)	0.606
Travel	8 (6.6%)	14 (14.28%)	0.58
Immobilisation	11 (9.09%)	25 (25.51%)	0.59
Active cancer	1 (0.82%)	5 (5.1%)	0.69
Oral contraceptive use	2 (1.65%)	5 (5.1%)	0.48
Postpartum	0	2 (2.04%)	0.39
Pregnant	0	3 (3.06%)	0.29
Surgery	17 (14.04%)	22 (22.44%)	0.28
Trauma	2 (1.65%)	4 (2.89%)	0.48

Values are mean ± SD, median (interquartile range), or n (%).

Table 2 Baseline clinical characteristics of treatment groups and laboratory data

	rt-PA + (n = 121)	**rt-PA - (n = 98)**	**p value**
Systolic blood pressure, mm Hg	90 (50-90)	120 (95-180)	<0.001
Dyastolic blood pressure, mm Hg	60 (40-80)	72 (50-70)	<0.001
Wells score	6(0-10)	4.5(0-10)	<0.001
D-Dimer (ng/mL)	6184 (272-10000)	4797 (823-10000)	0.007
Troponin T (pg/mL)	80 (0-4017)	30 (0-945)	<0.05
ProBNP (pg/mL)	2450 (26-8032)	1110 (0-17887)	0.02
CK-mb	2.3 (0-401)	1.5 (0-27)	0.04
CK	69 (1-2810)	62 (0-925)	0.80
Concomitant DVT	31(25.61%)	49 (36.3%)	0.28
Echocardiographic findings			
Right ventricular dysfunction	73 (60.33%)	60 (61.22%)	>0.05
Systolic PAB, mm Hg	58 (30-100)	50 (25-100)	<0.001

Abbreviations: ProBNP= pro-brain natriuretic peptid, CK: creatine kinase, CK-MB: creatine kinase-muscle/brain. Values are mean ± SD, median (interquartile range), or n (%).DVT: Deep Venous Thrombosis, PAB: Pulmonary Arterial Pressure

Cerebral hemorrhage observed in 1 case (0.83%) in group 1, 2 case (0.98%) in group 2 and 1 case (0.62%) in group 3 (p>0.05). Gastrointestinal system (GI) bleeding happened 2 cases (1.65%) in group 1 and 2 cases (0.98%) in group 2 (p>0.05). Minor bleeding was observed at similar rates due to the treatments (Table 3). Fatality due to hemorrhage was not observed.

Table 3 Hemorrhage types due to treatment in the cases

Hemorrhage	Grup 1 (rt-PA) n =121* n(%)	Grup 2 (enoxoparin) n=205** n(%)	Grup 3 (warfarin) n=159 n(%)	p
Major	1 (0.83)	2 (0.98)	1(0.62)	>0.05
Intra cranial bleeding(ICH)	1 (0.83)	2 (0.98)	1 (0.62)	0.37
Hemoglobin drop of ≥5g/dL Fatal bleeding	-	-	-	
Minor	2(1.65)	2 (0.98)	_	>0.05
Hemoglobin drop of 3 to 5 g/Dl GIS bleeding	2(1.65)	2 (0.98)	-	0.69
Requiring medical attention	6 (4.96)	5 (2.44)	8 (5.02)	>0.05
Hematuria	3 (2.48)	4 (1.95)	5 (3.14)	0.55
Intraocular bleeding	3 (2.48)	1 (0.49)	3 (1.88)	0.29
Minimal	4 (3.31)	1 (0.49)	1 (0.62)	0.36
Intervention site	4 (3.31)	1 (0.49)	1 (0.62)	0.36
Total	13 (10.75)	10 (4.89)	10 (6,26)	>0.05

Abbreviations: rt-PA: Recombinant Tissue Plasminogen Activator, GI: Gastrointestinal Values are n (%); * 121 patients receiving rt-PA continued the treatment with enoxaparin; ** Of the 205 patients who received enoxaparin, 159 received warfarin whereas 46 patients continued using enoxaparin.

The study groups have followed up for five years. Recurrent pulmonary embolism, residual chronic thrombus, chronic PE, and deaths were documented in the first month, first year, and fifth-year (Table 4). There is no difference in terms of recurrent pulmonary embolism, residual chronic thrombus, chronic PE, and death in the rt-PA receiving group compared with the non-rt-PA receiving group (Table 5).

Table 4 Death, recurrence, chronic PE and residuel chronic thrombus ocurred on the 1st mounth,1st and 5th year after first PE

	rt-PA + n = 121(%)	rt-PA - n = 98(%)	p
Death			
1st month death	8 (6.61%)	11 (11.22%)	0.31
1st month death-1st Year death	19 (15.70%)	24 (24.48%)	0.17
1st Year death -5 years follow up	13 (10.74%)	12 (12.24%)	0.66
Recurrence	8 (6.61%)	2 (2.04%)	0.08
Thrombophilia	3 (2.47%)	1 (1.02%)	
Chronic PE	3 (2.47%)	5 (5.10%)	0.21
Residuel Chronic Thrombus (DVT)	5 (4.1%)	1 (1.02%)	0.62
Chronic Thrombus on admission	4 (3.3%)	0	

Abbreviations: rTPA: Recombinant Tissue Plasminogen Activator, PE: Pulmonary embolism, DVT: Deep venous thrombosis.

Table 5 1st month causes of death

Causes of death within the first 30 days	rt-PA + (n = 121)	rt-PA – (n = 98)
Due to PE	4 (3.44%)	5 (4.85%)
Other reasons	4 (3.44%)	6 (5.82%)
Sepsis	2 (1.72%)	0
Chronic lung disease	2 (1.72%)	1 (0.97%)
Chronic heart failure, arrhythmia	0	3 (2.91%)
Cancer	0	1 (0.97%)
Stroke	0	1 (0.97%)
Total	8 (6.88%)	11 (10.67)

4. Discussion

Studies based on two large, multicenter registries reported that patients with right ventricular dysfunction due to pulmonary embolism had increased rates of in-hospital death, even in the absence of arterial hypotension or shock [11-13]. So for the other patients not having hypotension but having the risk of mortality thrombolysis can be applied after a careful risk-benefit assessment.

The way and the criteria of thrombolytic therapy of these intermediate-risk patients are mostly reported in ESC 2014 guideline but still the number of patients who had thrombolysis is lower than that should be. The reason for this is the feary complication of intracranial hemorrhage of thrombolysis. The reported prevalence of intracranial hemorrhage, based on pooled data, registry, or hospital experience, ranged from 1% to 10%. But Konstandinides et all., Fasullo et al., Kucher et al., Sharifi et al reported none ICH [13-16] which rt-PA was the thrombolytic agent used in all these studies.

Kanter et al found ICH as 1.2%, after reviewing the data of 5 trials [17]. Fiumara et al reported 1.0% ICH [18]. Patients in the International Cooperative Pulmonary Embolism Registry (ICOPER) reported 3.0% ICH[19]. Dalen et al reported 2.1% ICH [20].

Stein et al. reviewed PE patients from Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality of hospital records in the USA and reported intracerebral hemorrhage as 1.0% among 27,900 stable patients who received thrombolytic therapy (21). The prevalence of intracerebral hemorrhage was found lower in the patients aged 65 years or less and without the renal disease [21-22].

The treatment of PE has followed a similar path to that of MI both in terms of therapeutic advancements and changes in management. Numerous very large randomized studies have been conducted about thrombolysis in ST-segment elevation MI (STEMI) [5, 7, 23].

Levine et al reviewed the hemorrhagic complications of thrombolytic therapy in both MI and venous thromboembolism and found a higher rate of bleeding associated with thrombolytic therapy in patients with PE compared with MI (24). Several meta-analyses have underlined the risk of bleeding associated with thrombolysis in PE [4, 6]. But, the available data of the studies used in the meta-analyses were limited in size, heterogen in patient selection and treatment regimens, and especially not standard for the definition of hemorrhage due to the treatment. Since there is a lot of hemorrhage description in the literature, standardization is important in this fact.

Intracerebral hemorrhage is 0.5-0.94 % risk following STEMI thrombolysis with rt-PA. A STEMI thrombolysis study ASSENT-2 showed that the ICH risk of TNK was 0.93% and rt-PA was 0.94% [7, 25]. We also found the risk of ICH 0.85 % in our PE patients who were treated by rt-PA. This result makes us think about the reasons for these different ICH incidence reports from multiple studies from 0% to 10%.

These are some studies done in the 1990s that provide evidence that thrombolytic therapy in PE has more major bleeding or ICH than other anticoagulants. Dalla Volta et al. Reported 15% major bleeding. Unfractionated heparin (UH)

was given after the thrombolytic therapy [26]. In Goldhaber reported 10.9 % major bleeding, 2.2% ICH with urokinase. In the rt-PA group, 2% ICH and 1% stomach hemorrhage were reported. In this study, UH was given immediately after thrombolysis and bleeding details include bleeding at the catheter site of the pulmonary angiography which was performed before and after the study [11]. In the study of Meyer et al. concomitant administration of UH and rt-PA were applied and there was not any ICH or GIS hemorrhage [27]. Until the study of Konstantinides et al in 2002 number of patients was under 100 and pulmonary angiography was applied to all patients for diagnosis and follow-up after thrombolysis [13].

In the PEITHO trial tenecteplase with UH were applied to 1006 patients with intermediate-risk PE with RV dysfunction, and a statistically significant reduction was found in morbidity and mortality within the 7 days compared to the UH-only group. In the UH-only group, 23 patients died despite 15 of them receiving tenecteplase as rescue therapy. Hemodynamic collapses were three times more frequent in the UH-only group (P=0.002) (3). Therefore, the PEITHO trial demonstrated that in patients with RV dysfunction, UH infusion without thrombolysis or delayed thrombolysis may increase mortality and morbidity. But this study also showed hemorrhagic stroke as 2% and major bleeds as 11% and the description of major bleeding were different from our study.

When all these studies were evaluated, it was thought that there are six main reasons for the high rates of ICH and major bleeding in patients with PE than the patients with STEMI in those receiving thrombolytic therapy:

UH, infusion with thrombolytic therapy or UH infusion after thrombolytic therapy was given in most of the studies. Also, major bleeding concepts are not common in the studies. Different thrombolytics have been used in the studies so different bleeding rates are possible. In most studies, the side effects of thrombolytic therapy were not compared with anticoagulation therapy. Anticoagulation with heparin infusion have risk of bleeding. Coumadin also increases the risk of bleeding. Until the study of Konstantinides et al in 2002 an invasive procedure: pulmonary angiography was applied to all patients for diagnosis and follow-up after thrombolysis. This may be the cause of interventional side major bleeding. In most of the studies, the number of patients was under 100 except for 3 studies [3, 13, 16].

According to the results of our study, the risk of ICH was 0.85% after thrombolysis by rt-PA. This result is close to the ICH ratio in patients receiving thrombolytic therapy in STEMI (0.63-0.94%) [28]. The hemoraghic events were evaluated according to the TIMI criteria [10].

In our study, the reasons for less major bleeding and ICH may be using rt-PA for the thrombolytic therapy of PE, not starting UH together or immediately after treatment. Also, we started LMWH treatment 12 hours after thrombolytic treatment, used proton pump inhibitors to prevent GIS bleeding and, performed as little invasive procedure as possible. The risk-benefit balance was assessed by paying attention to the contraindications, especially cooperation with neurology.

5. Conclusion

So, after finding the similar ICH rates in thrombolysis of ISTEMI and PE as a result of our study like some other studies we discussed above, we thought that the higher rates of bleeding and ICH under thrombolysis in PE versus MI may be only a minth. Thrombolysis trials in MI have been very large, while the majority of PE trials have not exceeded 100 patients. Thrombolytic therapy was associated with lower all-cause mortality in patients with PE, including the patients with hemodynamically stable PE associated with RV dysfunction. However, thrombolytic therapy is being applied below the level that it should be. The primary reason for this is the fear of ICH. The risk-benefit assessment, may be made by taking cardiologists as a referance since PE can be as lethal as MI.

Compliance with ethical standards

Acknowledgments

Intellectual content was planned by HCH, HK, EA; data were scanned by HH, EB, ME, ES, OA, AK; data were analyzed by DO; the manuscript was written by HCH, HK; the manuscript was edited by HCH, HK, EA.

Disclosure of conflict of interest

All authors disclose that they haven't any conflict of interest. The authors report no competing interests. The authors alone are responsible for the content and writing of this paper.

Statement of informed consent

There is no informed consent due to the study was retrospective design.

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