

Tenecteplase compared with streptokinase and heparin in the treatment of pulmonary embolism: an observational study

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ABSTRACT

Background: Thrombolytics are recommended in high risk patients with massive pulmonary embolism (PE). However, clinical practice seems to be far different and questions related to its utility in less severely affected patients remain the subject of investigation. The objective of this observational study was to compare the efficacy and safety of tenecteplase with streptokinase and heparin.

Method: A total of 103 patients (tenecteplase: 62, streptokinase: 17, heparin: 24) diagnosed with PE (massive: 33 [32.04%], submassive: 50 [48.54%], and minor: 20 [19.42%]) were included.

Results: Mean age was 50.04 years and major risk factors were immobilization due to hospitalization, history of deep vein thrombosis, and diabetes. Common clinical symptoms of dyspnoea, right ventricular dysfunction, and cough were found in 94.17%, 81.55%, and 77.67% patients, respectively. Between treatment and day 7, death occurred in 4.84%, 5.88%, and 8.33% patients in the tenecteplase, streptokinase, and heparin groups, respectively. The differences among treatment groups were non-significant ($p > .05$). All treatments have demonstrated significant alleviation of dyspnoea and heart rate ($p < .05$). Significant ($p < .05$) increase in oxygen saturation was seen and it was markedly higher in the tenecteplase-treated patients compared with the streptokinase- and heparin-treated patients. By day 7, there was 100% resolution of right bundle branch block only in the tenecteplase group. No intracranial bleeding or fatal bleeding episodes were found in any group.

Conclusion: Tenecteplase was found to be effective in patients with PE irrespective of their clinical status and no major adverse events were noted.

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Introduction

Pulmonary embolism (PE) is a well-recognised common life threatening condition that is often difficult to detect. It is the most serious clinical presentation of venous thromboembolism and in majority of cases is the consequence of deep vein thrombosis [1]. Direct obstruction or occlusion of the pulmonary arteries and release of potent vasoconstrictors leads to quick rise in pulmonary vascular resistance. Due to this right ventricular (RV) contractile function is compromised and ensues its failure. This vicious cycle of cardiogenic shock is augmented by concomitant hypoxia, which inevitably leads to cardiovascular collapse and death [2,3].

The global incidence of PE is estimated to be 60–70 per 100,000 of the general population and ranks third among the most common types of cardiovascular disease [4,5]. The mortality rate is 8–10% in treated patient and is as high as 25–30% in untreated patients [6]. Nearly 25% of patients die within the first hours of presentation and the actual figures can be even higher as patients who die before diagnosis usually do not get accounted [7]. Associated with significant

morbidity and mortality, early diagnosis and timely treatment is of paramount importance to ensure the highest quality of care.

Appropriate treatment regimen can be best selected using risk stratification primarily by assessing hemodynamic impact, extent of PE, the patient's clinical status and potential risks of the therapy [5]. Depending on PE presentation, that is, submassive (25–50% obstruction), massive (>50% obstruction), or minor, initial treatment is primarily focused on restoring adequate blood flow through the pulmonary bed reversing RV failure and preventing PE recurrence [8]. Anticoagulation is an effective treatment and heparin is known to reduce both mortality and the incidence of recurrent PE. Although anticoagulants do not directly dissolve pre-existing clot, they prevent clot propagation and indirectly decrease clot burden by allowing endogenous fibrinolytic activity to dissolve existing thromboemboli. The rate at which this process occurs is variable and in many patients resolution is incomplete after several months. Thrombolytic therapy (streptokinase, urokinase, alteplase, and tenecteplase) on the other hand, with its

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ability to produce rapid clot lysis offers an effective alternative and result in faster improvement in pulmonary perfusion, hemodynamic alterations, gas exchange with lesser incidence of recurrent PE. It also has shown to improve survival, especially in patients with high risk PE [9,10].

Tenecteplase is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. It has three amino acid substitutions, which decrease plasma clearance, increase fibrin specificity and resistance to plasminogen activator inhibitor-1 (PAI-1). The modifications to tenecteplase allow the drug to be administered as a single intravenous bolus over 5 s [11,12].

Despite the critical nature of PE, to date fewer randomized clinical trials comparing thrombolytic agents versus heparin are conducted. Further literature search did not reveal any study comparing tenecteplase with streptokinase and heparin. Comparative studies with use of these agents are very limited and if available, the sample size is small. Thrombolytics are recommended in high risk patients with massive PE, its utility in lesser severe patients remain subject of investigation. All these conditions influenced us to conduct a study on tenecteplase comparing it with streptokinase and heparin in managing PE. The objective of the present study was to compare the efficacy and safety of tenecteplase with streptokinase and heparin.

Methods

Anticoagulation with unfractionated and low molecular weight heparin has shown to improve outcome in pulmonary embolism [1]. Thrombolytic therapy has a potential to produce faster thrombolysis, improve hemodynamic instability, and eliminate the venous thrombi [2].

Despite the approval of streptokinase, urokinase, and alteplase for thrombolysis in PE, the efficacy of these thrombolytics remain unclear due to the high mortality associated with this condition and lack of large randomized controlled trials [3,4].

Tenecteplase is a third generation thrombolytic with longer plasma half-life, better fibrin specificity, and higher resistance to inhibition by plasminogen-activator than alteplase [5].

This was an observational study conducted at Krishna Institute of Medical Sciences (KIMS) Hospital, Hyderabad, India. The protocol was approved by the Ethics Committee of KIMS and the study was conducted in accordance with the Declaration of Helsinki. Data of all hospitalized patients >18 years of age diagnosed with PE from January 2008 to December 2014 and treated with tenecteplase, streptokinase, or heparin were included for analysis. The data were obtained from the medical record and only confirmed cases of PE were considered. The patients were diagnosed to have PE if there was evidence of thrombus as documented by CT pulmonary angiogram with or without D-dimer testing.

The exclusion criteria included patients with active visceral bleeding or spontaneous intracranial haemorrhage or those with a history of cardiopulmonary resuscitation, chronic pulmonary hypertension or severe COPD, patients with

minimally controlled severe hypertension or diabetic hemorrhagic retinopathy, and pregnant patients.

Treatment

Tenecteplase was given as an intravenous weight adjusted bolus over 5 s at a dose ranging from 30 to 50 mg (0.5 mg/kg), with a 5 mg step-up for every 10 kg increase from 60 to 90 kg. For streptokinase, a loading dose of 250,000 units was infused into a peripheral vein over 30 min followed by 100,000 units/h for 24 h (72 h if concurrent DVT was suspected). Unfractionated heparin was administered intravenously as an initial bolus of 80 U/kg or 5000 U followed by an infusion of 18 U/kg/h or 1300 U/h till patient condition was stabilized.

The decision for the treatment of minor severity pulmonary embolism patients was completely at the discretion of the health care professional based on the CT angiogram reports and/or D-dimer report. However, comparable number of patients with low risk of pulmonary embolism were distributed in all the groups. Also, in clinical practice based on our observation, all patients irrespective of their clinical status of PE (minor, submassive, massive) are treated either with tenecteplase, streptokinase, or heparin. This is contrary to the recommendations for the use of thrombolytics in only hemodynamically compromised patients.

Assessment

All patients were followed for 180 days. Patient's baseline data such as mean, age, gender, weight, disease characteristics, predisposing factors, etc were collected from their records. Patients with confirmed diagnosis of PE were classified as massive if there was evidence of hemodynamic compromise (defined as systolic BP <90 mmHg) and as submassive if there was right ventricular dysfunction on echocardiography with no hemodynamic compromise. Patients without any evidence of these features were labelled as minor PE cases.

The primary efficacy outcome was death from any cause within 7 days of treatment. Pulmonary embolism and major adverse cardiac events were considered and accounted for the deaths. There were no other cause. The secondary outcome included death within 180 days, changes in prognostic factors after the therapy such as dyspnoea, blood pressure, heart rate, right bundle branch block (RBBB), and oxygen saturation (SaO₂) at 7 days and 180 days.

Safety was assessed by evaluating adverse outcome especially bleeding complications. Bleeding was classified as major if there was any intracranial bleeding or overt bleeding with decrease in haemoglobin ≥ 3 g/dL. Other events such as hematuria or hematemesis were considered minor. The patients were followed up to 180 days.

Statistical analysis

Baseline characteristics of patients are described according to treatment received. Continuous variables are summarized

Table 1. Baseline characteristics of the patients.

Parameters	Tenecteplase (n = 62)	Streptokinase (n = 17)	Heparin (n = 24)	Total (N = 103)
Age, years	50.17 ± 14.74	47.11 ± 15.33	52.83 ± 19.00	50.04 ± 16.36
Male, n (%)	40 (64.5)	12 (70.5)	14 (58.3)	66 (64.08)
Weight, kg	82.5 ± 15.88	65.3 ± 9.51	71.9 ± 11.19	73.23 ± 12.19
BMI, kg/m ²	30.18 ± 5.7	24.06 ± 2.63	26.11 ± 3.33	26.78 ± 3.89
Predisposing factors, n (%)				
History of DVT	29 (46.77)	8 (47.06)	13 (54.17)	16 (48.54)
Smoking	7 (11.2)	3 (17.6)	3 (12.5)	13 (12.63)
Surgery	9 (14.5)	2 (11.76)	3 (12.5)	14 (13.59)
Hospitalization	31 (50.0)	6 (35.29)	15 (62.5)	52 (50.49)
Malignancy	6 (9.6)	0 (0)	5 (20.83)	11 (10.68)
DM	13 (20.9)	2 (11.76)	6 (25)	21 (20.39)
Diagnosis, n (%)				
Minor	13 (20.96)	2 (11.76)	5 (20.83)	20 (19.42)
Sub-massive	25 (40.32)	14 (82.35)	11 (45.83)	50 (48.54)
Massive	24 (38.70)	1 (5.8)	8 (33.33)	33 (32.04)

using descriptive statistics, that is, number of subjects, mean, and standard deviation (SD). Qualitative variables are summarized by frequency and percentage. Student's *t*, Chi square, or Fisher's exact tests were used to measure the association between clinical variables and the endpoint. Fisher exact test was used if there were more than 20% of cells with an expected value of <5 in a table.

Results

Demographic and baseline characteristics

A total of 103 patients diagnosed with pulmonary embolism were identified and included for analysis into the study. Their mean age was 50.04 years. Majority of the patients were males 66 (64.08%). The major predisposing factors were immobilization as a result of hospitalization, history of DVT, and diabetes (Table 1). The most common clinical symptoms were dyspnoea (94.17%) followed by right ventricular dysfunction (81.55%) and cough (77.67%). Massive, submassive, and minor PE was diagnosed in 33 (32.04%), 50 (48.54%), and 20 (19.42%) patients, respectively. All patients were treated with tenecteplase, streptokinase, and heparin. Details baseline characteristics of the patients according to treatment group are presented in Table 1.

Primary efficacy parameter

Death: Between treatment and day 7 data, death occurred in three (4.84%) patients in the tenecteplase group as compared with one (5.88%) in the streptokinase group and two (8.33%) in the heparin group. By day 180, six (9.67%) patients in the tenecteplase group had died as compared with two (11.76%) in the streptokinase group and three (12.5%) in the heparin group. The difference between treatment groups was non-significant ($p > .05$) at both the time points.

Secondary efficacy parameters

Data on improvement in the secondary parameters are presented in Table 2. After treatment, all the three treatment groups have shown significant improvement in the rate of

Table 2. Improvement in secondary efficacy parameters.

Parameters	Time	Tenecteplase (N = 62)	Streptokinase (N = 17)	Heparin (N = 24)
Dyspnoea*, n	Pre	60 (96.77)	15 (88.23)	22 (91.67)
	Post	35 (56.45)	9 (52.94)	16 (66.67)
	Day 7	0 (0.0)	1 (5.88)	1 (4.17)
	6 months	3 (4.84)	2 (11.76)	2 (8.33)
RBBB, n	Pre	11 (17.74)	6 (35.29)	1 (4.17)
	Post	1 (1.61)	2 (11.76)	0
	Day 7	0	2 (11.76)	1 (4.17)
Heart rate*, Bpm	Pre	108.34 ± 22.12	107.56 ± 17.32	101.41 ± 23.91
	Post	84.21 ± 18.10	98.54 ± 7.23	90.77 ± 16.21
	Day 7	79.45 ± 10.04	92.08 ± 10.34	90.23 ± 10.08
	6 months	78.11 ± 7.02	89.32 ± 11.21	87.58 ± 8.32
Systolic BP, mmHg	Pre	118.01 ± 23.21	124.46 ± 16.10	126.21 ± 27.78
	Post	128.41 ± 20.05*	127.31 ± 17.97	124.43 ± 24.05
	Day 7	129.30 ± 13.45*	126.02 ± 16.54	126.91 ± 21.04
	6 months	128.31 ± 13.98*	122.58 ± 16.21	124.44 ± 18.23
Diastolic BP, mmHg	Pre	79.05 ± 14.23	77.06 ± 10.53	80.07 ± 11.23
	Post	79.68 ± 11.68	79.57 ± 10.99	86.34 ± 8.09
	Day 7	80.01 ± 9.41	78.33 ± 10.54	82.78 ± 9.45
	6 months	81.28 ± 10.56	80.45 ± 13.87	80.77 ± 10.24
SaO ₂ *, %	Pre	88.79 ± 10.03	91.90 ± 4.10	91.4 ± 3.38
	Post	96.90 ± 4.10	94.90 ± 2.31	92.75 ± 2.75
	Day 7	97.46 ± 2.00*	92.72 ± 2.00	90.25 ± 1.65
	6 months	97.91 ± 1.70*	90.09 ± 8.50	91.83 ± 1.74

* $p < .05$ compared to baseline value.

dyspnoea at all evaluations compared with baseline data ($p < .05$). Greater percentage of patients receiving tenecteplase showed improvement compared with those receiving streptokinase and heparin. However, the difference between the treatment groups was not significant ($p > .05$).

RBBB was observed in more number of patients in the tenecteplase and streptokinase groups compared with heparin. By day 7, there was 100% resolution of RBBB only in the tenecteplase group. In the streptokinase group, two of the six patients observed at baseline continued to have RBBB at day 7, whereas there was no resolution in RBBB observed in one patient who was treated with heparin.

Significant reduction in heart rate was seen post treatment in all three treatment groups ($p < .05$). The reduction in heart rate from baseline was more in tenecteplase treated patient compared with streptokinase and heparin treated patients. The difference in heart rate reduction in the tenecteplase group compared with streptokinase and heparin was statistically significant ($p < .05$).

Systolic blood pressure increased significantly from baseline only in the tenecteplase treated patients and no significant change was seen in the streptokinase and heparin groups. Also, there was no significant change from baseline in the diastolic blood pressure in any of the treatment groups.

Increase in the oxygen saturation was significant ($p < .05$) and markedly higher in the tenecteplase treated patients compared with the streptokinase and heparin treated patients.

Safety evaluation

Bleeding complications were noted at day 7 after the treatment. The incidence of overall bleeding in the three groups

was comparable [tenecteplase: 2 (3.2%), streptokinase: 1 (5.88%), heparin: 1 (4.17%)]. No intracranial bleeding or fatal bleeding episode was found in either group.

Discussion

The clinical course and prognosis of PE patients vary widely and is life threatening. For example, in patients with massive PE, 50%, 70%, and 85% of patients die within 30 min, 1 and 6 hours of the onset of symptoms, respectively [13]. Despite initiating treatment with anticoagulation, 8–17% of patients experience failure or recurrence after 3–6 months [14–16]. On the other hand, thrombolytic therapy directly dissolves the thrombi and more rapidly reverses hemodynamic instability compared with anticoagulant therapy. The current guidelines recommend the use of thrombolytics only in high risk patients with massive PE associated with circulatory collapse [1]. Questions related to its utility in lesser severe patients remain subject of investigation as clinical practice seems to be far different from the recommended guidelines. Tenecteplase is an alteplase molecule, and apart from application in treatment of massive PE, its use has also been documented in submassive and hemodynamically stable patients of PE with right ventricular dysfunction [17,18]. There are fewer studies on tenecteplase use in pulmonary embolism till date.

All patients irrespective of their clinical status of PE (minor, submassive, massive) were treated either with tenecteplase, streptokinase, or heparin. This was contrary to the recommendations for the use of thrombolytics in only hemodynamically compromised patients. However, studies have been reported with use of tenecteplase in hemodynamically stable patients as well with favourable results [17,19]. The major risk factors for PE in the present study were history of DVT, hospitalization, and diabetes.

In the present study, death occurred in 4.84%, 5.88%, and 8.33% and 9.67%, 11.76%, and 12.5% patients in the tenecteplase, streptokinase, and heparin groups by day 7 and 180, respectively. Though the difference between treatment groups was non-significant ($p > .05$), tenecteplase was found to produce numerically better results than the other two. The result could have been different if the treatment group would have been balanced with respect to the number of patients. Since this was an observational study, we did not have control on the number of patients in each group. More number of patients was assigned to tenecteplase compared with that of streptokinase and heparin, which is also suggestive of the preference of physician for tenecteplase. Thrombolytic therapy is known to significantly reduced mortality in submassive PE compared with heparin anticoagulation alone [20]. In addition, all patients subsequent to treatment showed significant improvement in clinical symptom of PE, that is, dyspnoea, heart rate, and oxygen saturation. The difference between the groups was not significant but greater percentage of patients in the tenecteplase group shown improvement when compared with streptokinase and heparin. Similarly, in a study reported by Shukla et al., tenecteplase was found to be effective and safe in the treatment

of PE. In this study, all the 30 patients who received weight-adjusted tenecteplase injection survived with the improvement in symptoms like dyspnoea, chest pain, and syncope [21]. Another study demonstrated favourable efficacy of tenecteplase in 41 patients with suspected or confirmed acute pulmonary embolism. In the 40 survived patients, there was reduction of dyspnoea, hemoptysis, tachycardia ($p < .0001$), and increase in the oxygen saturation (SaO_2) ($p < .0001$). Hypotension recovered in all patients till the time of discharge and there was a significant reduction in right ventricular systolic pressure in all 18 patients who underwent 2-D echocardiography both before and after the tenecteplase therapy [18]. Use of tenecteplase offers several advantages such as single boluse dose that allows more formation of plasmin, which may allow rapid clearance of clot and resolution of symptoms. Also, there is no requirement of continuous infusion and offer great therapeutic convenience in thrombolysis as against the older thrombolytics.

Treatment with thrombolytic is known to carry a risk of major bleeding, including intracranial hemorrhage. Clinically relevant non-major bleeding was observed in 3.2% of patients in the tenecteplase group, 5.88% in the streptokinase group, and 4.17% of patients in heparin group. No intracranial bleeding or fatal bleeding episode was observed in any treatment groups. Literature reports a wide range of incidence for major bleeding (0–33%) and intracranial hemorrhage (0–7.4%); the wide range is because of the small sample sizes of many of these studies [22,23]. In a meta-analysis that included 16 studies ($n = 2115$), incidence of major and intracranial bleeding was 9.24% and 1.46%, respectively and was also significantly more compared with anticoagulant therapy [24].

Conclusion

The present study demonstrated that thrombolytic and anti-coagulant therapies both are safe. However, therapy can be tailored as per the clinical status of the patient. Anticoagulants can always be the drug of choice in mild conditions, whereas consideration should be given to the use of thrombolytic in moderate to critically ill patients. There are some limitations with our study and should be taken into consideration. Being an observational study we did not had control on treatment assignment and nor on the number of patients in each treatment group. There were unequal number of patients in each treatment group and this might have some impact on the results of the study. Considering lack of studies in patients with PE, this data can be useful in planning larger trials that can influence treatment and management of these patients.

Transparency

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards. The protocol was approved by the Ethics Committee of KIMS and the study was conducted in accordance with the Declaration of Helsinki.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of interest

All authors declare that they do not have any conflicts of interest. JDA peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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