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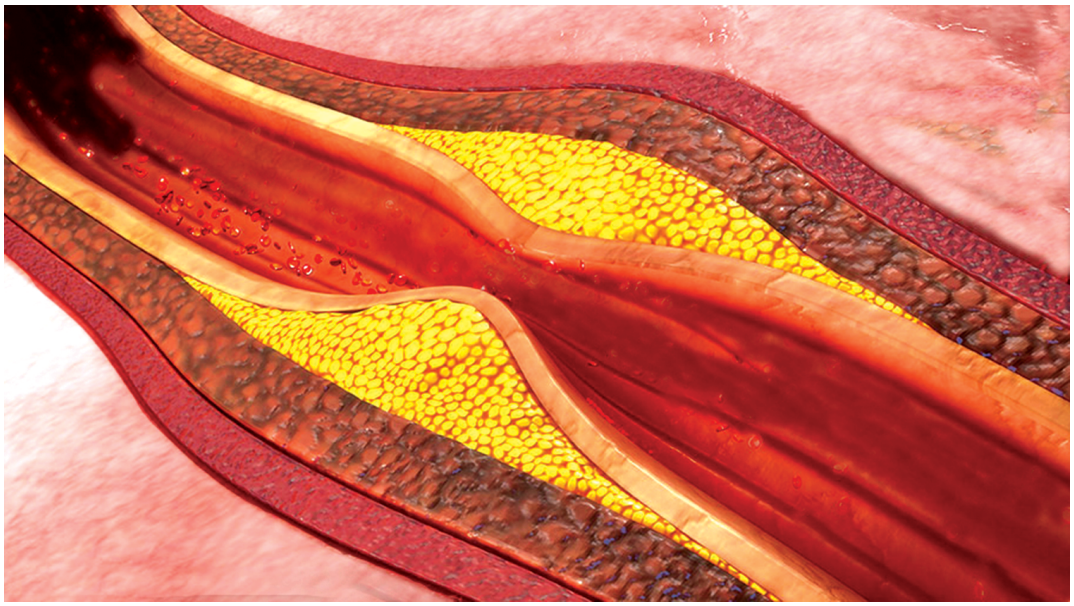

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Thrombolysis in Acute Pulmonary Embolism: Are we overdoing it?

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ABSTRACT

Aim and Methods: We aimed to study the clinical data and outcome of patients admitted in our center with acute pulmonary embolism (PE) over a 5-year period from May 2013 to April 2018. The main outcome data included were: in - hospital bleeding, in - hospital right ventricular (RV) function improvement, pulmonary arterial hypertension improvement, duration of hospital stay, and 30- and 90-day mortality.

Results: A total of 114 (69 m, 55 f) patients with the mean age of 55 ± 15 years were included. Patients who had involvement of central pulmonary trunk called as "Central PE" group (n = 82) and others as "Peripheral PE" group (n = 32). There were more women in the peripheral PE group (53.1% vs. 34.1%, P = 0.05), while RBBB (22% vs. 3.1%, P = 0.02) and RV dysfunction (59.8% vs. 25%, P = 0.002) were noted more in the central PE group. Systemic thrombolysis was done in 53 patients (49 central, 4 peripheral), of which only 3 had hypotension and 28 patients were in the Intermediate-high risk group. The overall inhospital, 30-day, and 90-day mortalities were 3.6, 13.2, and 22.8%, respectively. Bleeding was significantly higher in the thrombolysis group compared to the nonthrombolysis group (18.9% vs. 0, P = 0.0003). However, improvement in pulmonary hypertension was noted more in thrombolysis group compared to nonthrombolytic group (49% vs. 21.2%, P = 0.01).

Conclusion: This retrospective data from a tertiary center in South India showed that short- and mid-term mortality of patients with PE still remains high. The high nonguideline use of thrombolysis has been reflected in the increased bleeding noted in our study.

Key words: Bleeding, central pulmonary embolism, peripheral pulmonary embolism, pulmonary embolism, thrombolysis

INTRODUCTION

Acute pulmonary embolism (PE) is a common, potentially life-threatening disease and is the most serious clinical presentation of venous thrombo-embolic disorder.[1] Mortality occurs in approximately 2%–6% of patients in hemodynamically stable PE and in 30% or more in patients with hemodynamic instability or shock.[2-4] Of note, 25% of the patients do not survive the 1st year after diagnosis of PE, although the majority of deaths during this time are related to underlying conditions such as cancer or chronic heart disease rather than to PE itself.[3,4]

Over the past 25 years, thrombolytic therapy has consistently demonstrated improvement in hemodynamic parameters in patients with PE.[5] Clinically, although it results in reduced mortality in patients with massive PE, thrombolytic therapy is not beneficial in unselected patients with PE.[6,7] A review of randomized trials performed before

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2004 indicated that thrombolysis may be associated with a reduction in mortality or recurrent PE in high-risk patients who present with hemodynamic instability.[7] According to the European Society of Cardiology (ESC) guidelines on the diagnosis and management of acute PE published in 2014, the only current absolute indication for thrombolysis is high-risk PE (i.e., PE with shock or persistent hypotension).[8] In intermediate-risk patients, full-dose thrombolytic therapy can prevent potentially life-threatening hemodynamic decompensation, but this benefit is counterbalanced by a high risk of hemorrhagic stroke or major nonintracranial bleeding.[9] Even in the latest ESC guidelines published a few months ago, thrombolysis is indicated only in high-risk PE and to consider rescue thrombolysis in intermediate–high-risk PE patients.[10]

We aimed to study the clinical data including management decisions of patients presenting with acute PE in our center over a 5 years period and to analyze the clinical outcome of these patients to understand the "real-world" practice of management of PE in a high volume center in South India.

METHODS

Patients who were diagnosed to have acute PE by computed tomography pulmonary angiogram (CTPA) over a period of 5 years (May 2013 to April 2018 inclusive) in our center were identified by the electronic health-care database. All our hospital case records over the last 7 years were scanned and saved electronically in a database. We retrospectively analyzed the case records of these patients with their respective unique identification numbers. Their clinical data including baseline characteristics, imaging reports (ECHO/CTPA), clinical parameters, and management strategies (including thrombolysis) were recorded. A simplified PE Severity Index (PESI) score was calculated for all patients as per the guidelines.[11] The study has been approved by our Institutional Ethics Committee (Ref No-IEC-CS No-AMH-008/03-19) and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

Definitions

Central PE - PE involving the central pulmonary trunk (main pulmonary artery, Right or Left pulmonary artery).

Peripheral PE - PE involving peripheral pulmonary artery only.

Hypotension is defined as systolic BP < 90 mmHg Tachycardia is defined as heart rate > 100/min.

Right Ventricular (RV) dysfunction: Echocardiographic criteria of RV end-diastolic diameter of >30 mm or hypokinesia of RV free wall noted in any view or Tricuspid annular plane systolic excursion (TAPSE <16 mm).

Pulmonary arterial hypertension (PAH): By echocardiographic criteria of Right Ventricular Systolic Pressure (RVSP) - Normal <40 mmHg, mild PAH - 40-54 mmHg, Moderate PAH - 55-69 mmHg, Severe PAH - >70 mmHg.

Outcome data

The main outcome data included were inhospital mortality, 30-day mortality, 90-day mortality, inhospital bleeding, duration of hospital stay, improvement in PAH, and improvement in RV function during hospital stay. PAH improvement is defined as at least one-step improvement of PAH in the echocardiogram prior to discharge, compared to the index echocardiogram. Except for 30-day and 90-day mortality, all other outcome data were from the index admission and were obtained from the records.

For 30-day and 90-day mortality, we scanned the patients' follow-up visit to the hospital (to any department) with the unique ID number and considered them alive if they have visited the hospital. If the details were not available, patients were contacted through phone and mail to receive further information.

Statistics

Continuous data were presented as mean ± standard deviation and categorical outcomes were presented as percentages. Categorical outcomes were compared by means of Fisher's exact test and permutation unpaired *t*-test was used to compare continuous variables between two groups. $P = 0.05$ was considered to be statistically significant.

RESULTS

A total of 114 (69 males, 55 females) patients with the mean age of 55 ± 15 years were diagnosed with acute PE by CTPA during the study period. Eighty-two patients were grouped as "central PE" and the other 32 patients as "Peripheral PE" group. The baseline characteristics of the two groups are compared in Table 1. There were more women in the peripheral PE group (53.1% vs. 34.1%, $P = 0.05$), while RBBB (22% vs. 3.1%, $P = 0.02$) and RV dysfunction (59.8% vs. 25%, $P = 0.002$) were noted more in the central PE group.

A total of 53 patients received thrombolysis for PE (49 in central and 4 in peripheral PE group), of which alteplase is the most commonly used agent [Table 2].

Vitamin K antagonists were used in 81 patients and novel oral anticoagulation in 30 patients. Three patients died before starting any oral anticoagulants. Apixaban is the most commonly used NAOC (14.9%) compared to dabigatran (3.5%) and rivaroxaban (7.9%). There

Table 1: Baseline characteristics and management strategy of central versus peripheral pulmonary embolism patients

	Total (*n*=114), *n* (%)	Central PE (*n*=82), *n* (%)	Peripheral PE (*n*=32), *n* (%)	*P*
Age (years)	55±15	56±15	52±16	0.15
Female	45 (39.5)	28 (34.1)	17 (53.1)	0.05
DVT	67 (58.8)	47 (57.3)	20 (62.5)	0.52
Hypotension	5 (4.4)	5 (6.1)	0	0.32
Tachycardia	64 (56.1)	48 (58.5)	16 (50)	0.53
RBBB	19 (16.7)	18 (22)	1 (3.1)	0.02
RV dysfunction	57 (50%)	49 (59.8)	8 (25)	0.002
Any PAH	72 (63.2)	55 (67.1)	17 (53.1)	0.19
Mild PAH	36 (31.6)	29 (35.4)	7 (21.9)	0.26
Moderate PAH	21 (18.4)	15 (18.3)	6 (18.8)	1.0
Severe PAH	15 (13.2)	11 (13.4)	4 (12.5)	1.0
No PAH	42 (36.8)	27 (32.9)	15 (46.9)	0.19

DVT: Deep-vein thrombosis, PAH: Pulmonary arterial hypertension, RV: Right ventricular, PE: Pulmonary embolism, RBBB: Right bundle branch block

Table 2: Management of patients with central and peripheral pulmonary embolism

	Total (*n*=114), *n* (%)	Central PE (*n*=82), *n* (%)	Peripheral PE, (*n*=32), *n* (%)	*P*
Thrombolysed	53 (46.5)	49 (59.8)	4 (12.5)	0.0001
Alteplase	42 (36.8)	40 (48.8)	2 (6.3)	0.0001
Tenecteplase	9 (7.9)	7 (8.5)	2 (6.3)	1.0
Streptokinase	2 (1.8)	2 (2.4)	0	1.0
IV heparin	38 (33.3)	27 (32.9)	11 (34.4)	0.83
LMWH	105 (92.1)	76 (92.7)	29 (90.6)	1.0
VKA	81 (71.1)	57 (69.5)	24 (75)	0.49
NOAC	30 (26.3)	23 (28)	7 (21.9)	0.64
Apixaban	17 (14.9)	13 (15.9)	4 (12.5)	0.78
Dabigatran	4 (3.5)	4 (4.9)	0	0.57
Rivaroxaban	9 (7.9)	6 (7.3)	3 (9.4)	0.70

VKA: Vitamin K antagonists, PE: Pulmonary embolism, IV: Intravenous, NOAC: Novel oral anticoagulants, LMWH: Low molecular weight heparin

Table 3: Clinical outcome of central versus peripheral pulmonary embolism

	Total (*n*=114), *n* (%)	Central (*n*=82), *n* (%)	Peripheral (*n*=32), *n* (%)	*P*
Inhospital bleeding	10 (8.8)	10 (12.2)	0	0.06
Duration of hospital stay (days)	7.5±3.9	7.3±3.7	8.1±4.3	0.6
PAH improvement	41 (36)	31 (37.8)	10 (32.3)	0.66
RV dysfunction improvement	4 (3.5)	2 (2.4)	2 (6.5)	0.30
Inhospital mortality	4 (3.6)	4 (4.9)	0	0.58
30-day mortality	15 (13.2)	10 (12.2)	5 (15.6)	0.76
90-day mortality	26 (22.8)	16 (19.5)	10 (31.3)	0.22

PAH: Pulmonary arterial hypertension, RV: Right ventricular

was no difference in outcome between the central and peripheral PE group [Table 3].

There was no significant difference in mortality between thrombolysis and nonthrombolysis groups [Figure 1]. Bleeding was significantly higher in thrombolysis group compared to the nonthrombolysis group (18.9% vs. 0%, *P* = 0.0003). There was one-step improvement in PAH in the thrombolysis group (50.9% vs. 23%, *P* = 0.003).

Out of those patients with central PE (*n* = 82), 49 were thrombolysed – the indication was high risk in 3 (6.1%), intermediate high in 28 (57.1%), but no clear indication in 18 (36.8%) patients. On comparing with central PE patients who did not receive thrombolysis (*n* = 33), the thrombolysis group had more patients with any form of PAH (77.6% vs. 51.5%, *P* = 0.02) or RV dysfunction (73.5% vs. 39.4%, *P* = 0.002) [Table 4].

Comparison of outcome of thrombolysis versus nonthrombolysis groups showed bleeding occurred more commonly in thrombolysed patients (20.4% vs. 0%, *P* = 0.004) with no difference in mortality or duration of hospital stay [Table 5]. However, PAH improvement was noted more in thrombolysis group compared to nonthrombolytic group (49% vs. 21.2%, *P* = 0.01). The bleeding rate was much higher in patients who had streptokinase (50%). Patients who had alteplase and tenecteplase had 16.7% and 22.2% bleeding, respectively.

Two patients who had central PE and hypotension were not thrombolysed (one due to previous intracranial

hemorrhage (ICH) and the other due to unknown reasons). Four thrombolysed patients in the peripheral PE group had it in the first year of the study (2013–2014), before proper guidelines were released.

Ten patients who were thrombolysed had some form of bleeding – 4 had gastric, 2 had rectal, one had ICH, one had hemoptysis, one had gum, and another one had conjunctival bleeding. Three patients who had gastric bleed and one who had rectal bleed needed red blood cell transfusion. One patient who had gastric bleed died while in hospital and another patient who had gastric bleed died within 90 days. The other eight patients were alive until 90 days of follow-up.

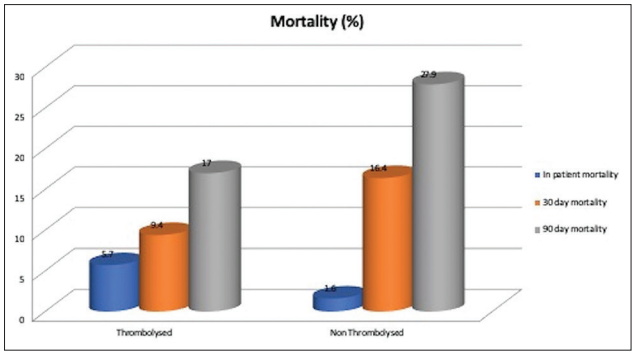

Figure 1: Mortality outcome of thrombolysed versus nonthrombolysed patients

DISCUSSION

This "real-world" study of patients with PE in a high-volume center suggests that thrombolysis was more commonly used than guideline-advised indications. In 18 patients in the central PE group who had thrombolysis (5 in the year 2013, 5 in 2014, 4 in 2015, 3 in 2016, and 1 in 2017), there was no clear indication identified from the medical notes of the patient for initiating thrombolysis. In general, there was a low threshold for giving thrombolytic treatment, particularly for patients with central PE, and this was adapted by most clinicians and hospitals until recent years.

Even though there was no significant mortality noted in this retrospective data from a high-volume center in patients who were thrombolysed, there was an increased risk of bleeding with thrombolytic therapy.

The latest ESC and the American College of Chest Physicians guidelines recommend thrombolysis only for those patients with clinical signs of hemodynamic decompensation.[8,10,12,13] The ESC, for example, classifies thrombolytic administration in patients with acute high-risk PE as a 1B recommendation, and the 2016 updated CHEST guidelines list it as a grade 2B recommendation.[8,12] The guidelines for thrombolysis in high-risk PE patient comes from randomized trials. A large meta-analysis done in 2004 showed that there were benefits in thrombolysing high-risk PE patients.[7]

There has been always a controversy about the use of thrombolytic therapy in intermediate-risk patients until

Table 4: Clinical characteristics of central pulmonary embolism patients who were thrombolysed versus nonthrombolysed

	Total (*n*=82), *n* (%)	Thrombolysed (*n*=49), *n* (%)	Nonthrombolysed (*n*=33), *n* (%)	*P*
Age	55.9±15.1	55.8±13.5	55.9±17.5	0.91
Female	28 (34.1)	17 (34.7)	11 (33.3)	1.0
RBBB	18 (22)	14 (28.6)	4 (12.1)	0.1
Any PAH	55 (67.1)	38 (77.6)	17 (51.5)	0.02
RV dysfunction	49 (60)	36 (73.5)	13 (39.4)	0.002
Hypotension	5 (6.1)	3 (6.1)	2 (6.1)	1.0
sPESI≥1	56 (68.3)	44 (89.8)	12 (36.3)	0.0001
Positive troponin	42 (51.2)	30 (61.2)	12 (36.3)	0.04
Intermediate high risk	34 (41.4)	28 (57.1)	6 (18.2)	0.0006

PAH: Pulmonary arterial hypertension, RV: Right ventricular, sPESI: Simplified pulmonary embolism severity index, RBBB: Right bundle branch block

Table 5: Outcome differences of central pulmonary embolism patients who were thrombolysed versus not thrombolysed

	Total (*n*=82), *n* (%)	Thrombolysed (*n*=49), *n* (%)	Nonthrombolysed (*n*=33), *n* (%)	*P*
Inhospital bleeding	10 (12.2)	10 (20.4)	0	0.004
RV dysfunction improvement	2 (2.4)	1 (2.0)	1 (3.03)	1.0
PAH improvement	31 (37.8)	24 (49.0)	7 (21.2)	0.01
Duration of hospital stay in days (mean±SD)	7.3±3.7	7±3	7.9±4.6	0.46
Inhospital mortality	4 (4.9)	3 (6.1)	1 (3.0)	0.64
30-day mortality	10 (12.2)	5 (10.2)	5 (15.2)	0.51
90-day mortality	16 (19.5)	8 (16.3)	8 (24.2)	0.41

PAH: Pulmonary arterial hypertension, RV: Right ventricular, SD: Standard deviation

the PE thrombolysis (PEITHO) trial was published.[14] PEITHO trial is a large randomized study which compared the outcome of intermediate-risk PE patients with or without thrombolysis. In this study, thrombolysis with tenecteplase showed a significant reduction in the risk of hemodynamic decompensation within 7 days. However, thrombolysis was also associated with a 10-fold increase in ICH (2% vs. 0.2%) and a five-fold increase in major hemorrhage (6.3% vs. 1.2%).[9] The follow-up results of the same study showed that thrombolysis with tenecteplase in intermediate-risk PE patients did not affect the long-term survival.[14] Despite this study publication in 2017, tenecteplase is not approved by FDA and ESC for usage in PE.

The ESC 2014 and 2019 guidelines recommend clinical risk assessment of those PE patients without hypotension by using The PESI score to further stratify the management strategy. Patients who have a PESI ≥1 are considered intermediate risk and further divided into intermediate–high-risk and intermediate–low-risk depending on RV function and laboratory tests such as natriuretic peptides and troponin. Those intermediate–high-risk patients can also be considered for rescue reperfusion therapy with thrombolytic agents. There is no other indication for thrombolysis in PE according to these guidelines.

Even in the latest published retrospective study from a single center in the US, only 15 out of 196 (7.6%) patients had thrombolytic therapy.[15] Out of the 15 patients, 4 are considered high risk and the other 11 were considered to be intermediate risk according to the PESI score. Alteplase is the only agent used in their study, as that is the only FDA-approved thrombolytic therapy for PE in the US.

Major extracranial bleeding occurred in 12 patients (6.1%) of the whole cohort in their study, but interestingly, only 2 out of 15 patients (13.3%) who received thrombolysis had bleeding. The other 10 patients who had major extracranial bleed did not undergo thrombolysis.[15]

In our study, thrombolysis rates were much higher at 46.5%. Out of the 53 patients who were thrombolysed, alteplase was used in 42 (79.2%), tenecteplase in 9 (16.9%), and streptokinase in 2 (3.7%) patients. Some form of bleeding occurred in 10 patients in our study, but all these 10 patients had thrombolytic therapy (18.9%), with zero bleeding in the nonthrombolytic group.

Limitations

We included only patients who had confirmed PE on CTPA. Patients with massive PE sometimes can present with sudden cardiac arrest with no time to undergo CTPA – a CT pulmonary angiogram (patient either died or had thrombolysis with echocardiographic findings). This particular group of patients was not included in our study. As this was a retrospective study, we did not have accurate data about these patients and therefore were not included.

CONCLUSION

This retrospective data from a tertiary center in South India showed that short- and mid-term mortality of patients with PE remains high despite early diagnosis and management. This study has shown that there was increased usage of thrombolytic therapy, even in those patients who did not fulfill the criteria for thrombolysis. This has led to a higher incidence of bleeding, even though some of them are nonlife-threatening bleeds. Clinicians should be aware of the indications for thrombolysis in PE and to risk stratify them accordingly in their day-to-day clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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