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RESEARCH ARTICLE

PULMONARY EMBOLISM – A PERSISTANT DILEMMA

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INTRODUCTION

Pulmonary embolism (PE) is a life-threatening condition with an incidence of about 60– 70 per 100 000 of the general population which is associated with significant morbidity and mortality[1]. PE remains a medical emergency ,in massive pulmonary embolism and consequent right ventricular failure, where restoration of pulmonary arterial flow is urgently required, prompt therapeutic intervention is imperative. Thrombolytic therapy has a potential to produce quick thrombolysis, improve hemodynamic instability and eliminate the venous thrombi [2].

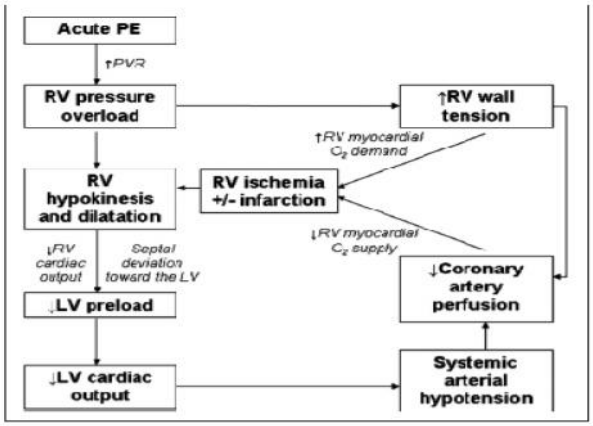

Figure 2. The pathophysiology of right ventricular (RV) dysfunction due to acute pulmonary embolism (PE). PVR, pulmonary vascular resistance; LV, left ventricular.

Despite the approval of streptokinase, urokinase, alteplase and tenecteplase for thromolysis in PE, the efficacy of these thromolytics remain unclear due to the high mortality associated with this condition [3, 4].

Pathophysology

Massive, Submassive, And Low-Risk Pe

The outcomes in PE vary substantially depending on patient characteristics.[5,6]

For ideal medical and interventional therapies for PE to the appropriate patients, definitions for subgroups of PE are required. The terms “massive,” “submassive,” and “low risk” have been described in the literature, although their definitions are vague, vary, and lead to ambiguity.[7]

Registry data have asserted that hypotension and circulatory arrest are associated with increased short-term mortality in acute PE. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the 90-day mortality rate for patients with acute PE and systolic blood pressure <90 mm Hg at presentation (108 patients) was 52.4% .[8]

Similarly, in the Germany-based Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) of 1001 patients with acute PE, in-hospital mortality was 8.1% for hemodynamically stable patients versus 25% for those presenting with cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation [9].Both the Geneva and Pulmonary Embolism Severity Index (PESI) clinical scores identify hypotension (blood pressure _100 mm Hg) as a significant predictor of adverse prognosis.[10,11]

Massive PE

Acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock)[12]

Submassive PE

Acute PE without systemic hypotension (systolic blood pressure

<90 mm Hg) but with either RV dysfunction or myocardial necrosis.

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RV dysfunction means the presence of at least 1 of thefollowing

- RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography
- RV dilation (4-chamber RV diameter divided by LVdiameter >0.9) on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of N-terminal pro-BNP (>500 pg/mL); or
- Electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)

Myocardial necrosis is defined as either of the following

- Elevation of troponin I (>0.4 ng/mL) or
- Elevation of troponin T (>0.1 ng/mL)[12]

Low-Risk PE

Acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE.[12]

Therapy for Acute Massive, Submassive, and Low-Risk PE

Patients with confirmed PE and no contraindications should receive prompt and appropriate thrombolysis therapy followed by subcutaneous lowmolecular- weight heparin (LMWH), intravenous or subcutaneous unfractionated heparin (UFH). For patients with suspected or confirmed heparin-induced thrombocytopenia, a non– heparin-based anticoagulant, such as danaparoid ,lepirudin, argatroban, or bivalirudin, should be used[13] Patients with intermediate or high clinical probability of PE should be given anticoagulant therapy during the diagnostic workup[14,15] Considerations about choice of chronic anticoagulant and duration of therapy are reviewed elsewhere[14,15]
The agent of choice for fibrinolysis has been a topic of controversy and debate till date. Various randomized trials have compared various thrombolytic regimens using rTPA, streptokinase, and urokinase, with rTPA being delivered over 2 hours and urokinaseand streptokinase delivered over 2–24 hours [16-21].

No one agent has proved superior[18]. rtPA regimens showed better pulmonary flow at 2 hours but not subsequently later when compared with long and short regimens of other agents.[17,19,21] Goldhaber[22] compared rTPA at a dose of 100 mg over 2 hours with the same agent at 0.6 mg/ kg over 15 minutes, and found similar improvements in all parameters as measured by echo, angiography, and VQ scan. Tebe[23] compared rTPA 100 mg over 2 hours with Reteplase (rTPA) 10 units at baseline and repeated at 30 minutes, and found no difference in all measured pulmonary haemodynamics.

In literature , no single agent or regimen has been shown to be more effective than any other. Though the theoretical risk of worsening hypotension with streptokinase in patients with circulatory compromise suggests that other thrombolytic agents may be preferable in specific cases.

Despite the theoretical advantages of higher local concentration at the clot site, the delivery of thrombolysis via pulmonary artery catheter offers no advantage in terms of mortality, morbidity, or haemorrhage risk over peripheral administration and carries the risks of a more invasive procedure[24]. Bolus therapy may be expected to produce more rapid thrombolysis with improved outcome but few trials found this method of administration offered no advantage over infusion regimens[22,25].

Thus presently the agent of choice and dosage still remains a dilemma The major complication of thrombolysis is haemorrhage, although allergy, hypotension, fever, nausea, and vomiting may occur[26]. The overall risk of haemorrhage with thrombolysis is reported as 6–20%, with no significant differences between the alternative agents.

The most feared bleeding complication is intracerebral haemorrhage, which has a reported incidence of 0.6–3%[27,28,29] The risk factors associated with intracranial bleeding are increasing age, increasing dose of thrombolytic, chronic hypertension, female sex, low body mass and pulmonary catheterisation[27-29]

Patients And Methods

The present study is a retrospective study documenting the use of thrombolytic agents in 140 cases of suspected and confirmed pulmonary embolism admitted in the last 5 years. All the patients had received thrombolysis in-hospital . Data obtained from case records of patients included findings of detailed medical history, clinical examination and investigations (echocardiography,CT pulmonary angiographies) performed. The outcomes were assessed in form of improvement in symptoms of dyspnoea and hemoptysis as well as improvement in heart rate, blood pressure, oxygen saturation, electrocardiogram , echocardiography and CT imaging . Well's criteria were used for assessment for pretest probability of pulmonary embolism [30].

RESULTS

The 140 cases admitted with suspected pulmonary embolism, only 68 % (96) patients were thrombolysed and rest 32% (44) were not thrombolysed due to old age, embolisation in smaller lobar vessels and affordability of the patients. Total enrolled patients were 105 males and 35 females of which 72 males and 24 females were thrombolysed .

Majority of the patients were in the age group 41-50 (56) followed by <30 (21) , 31-40 (35) , 51-60 (21) and 61-70(7) years The presenting symptoms of dyspnoea, chest pain, haemoptysis and syncope were found in 140 (100%), 7(5%) , 2(2.8%) and 28(20%) patients respectively. Patients had one or more risk factors for pulmonary embolism that included history of deep venous thrombosis or pulmonary embolism in past,

hospitalization or surgery or trauma in the preceding 4 weeks, diabetes mellitus, hypertension, smoking and air travel.

In the study, Table 1 shows the risk factors associated with PE in total and thrombolysed patients. 14 (10%) of all the thrombolysed patients had an associated hypercoagulable state including hyperhomocysteinemia, systemic lupus erythematosus, polycythemia vera, protein C deficiency and postpartum state.

Table 1	Total	Thrombolysed
DVT	88	53
Smoking	49	34
Hypertension	28	19
Diabetes mellitus	21	14
Malignancy	21	14
Hormone therapy	7	5
Previous hospitalization	20	19
Previous surgery	7	5
Previous stroke	3	2

Electrocardiography findings (Table 2) were noted as sinus rhythm , sinus tachycardia , Right bundle branch block (RBBB), S1Q3T3 in individual or in combination . The ECG findings included S1Q3T3 pattern (60%), right bundle branch block (15%), and ST-T changes (25%).

Table 2	Total	Thrombolysed
Sinus rhythm	14	10
Sinus tachycardia	35	24
Sinus tachycardia and rbbb	7	5
Sinus tachycardia and s1q3t3	70	47
Sinus tachycardia, rbbb and s1q3t3	14	10

21 patients (15%) had abnormalities in chest X-ray which included consolidation, decreased bronchovascular marking, haziness in the lung fields, signs of pulmonary hypertension and Hampton's hump.

According to Well's score for pretest probability of pulmonary embolism, 7 patients had high probability (Well's score>6), 80 patients had moderate probability (Well's score between 2 and 6) and 53 patients had low probability (Well's score<2).

The Wells score

Criterias	Points
clinically suspected DVT	3
alternative diagnosis is less likely than PE	3
tachycardia (heart rate > 100)	1.5
immobilization (≥ 3d)/surgery in previous four weeks	1.5
history of DVT or PE	1.5
hemoptysis	1.0
malignancy (with treatment within 6 months) or palliative	1.0

Traditional Interpretation

- Score >6.0 High (probability 59%)
- Score 2.0 to 6.0 Moderate (probability 29%)
- Score <2.0 Low (probability 15%)

Alternative Interpretation

- Score > 4 PE likely. Consider diagnostic imaging.
- Score 4 or less PE unlikely. Consider D-dimer to rule out PE..

The diagnosis of pulmonary embolism could be confirmed only in 101 (72%) patients using CT pulmonary angiography.

In others, pulmonary embolism was the most likely diagnosis based on Well's score, abnormal X-ray findings and evidence of right ventricular wall stress on 2D-echocardiography.

The signsof right heart failure documented were raised jugular venous pressure (46%), hepatomegaly (3%) and pleural effusion (5%). The baseline echocardiography findings included evidence of thrombus in dilated pulmonary artery, pulomonary artery (15%), right atrium (5%), dilated right ventricle (95%) and tricuspid regurgitation (55%) . (Table 3)
Of 96 patients that received thrombolytic therapy, 95patients survived. There was one case of mortality who was a 26 yrs old female of postpartum pulmonary thromboembolism with severe hypotension, cyanosis, bilateral crepitations in lungs and pulmonary hypertension. In the 95 survived patients, there was alleviation of dyspnoea and hemoptysis in all patients. Significant reduction in tachycardia and increase in the oxygen saturation (SaO2) was seen at the time of discharge as compared to at the time of presentation. Of 95 patients, 43 had hypotension (systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg) which recovered in all patients till the time of discharge (P\0.0001). There was resolution of right bundle branch block and there was a significant reduction in right ventricular systolic pressure in all the patients throughout the therapy on 2-D echocardiography. Resolution of pulmonary embolism on CT pulmonary angiography was also documented in majority of the patients.

Table 3	Total	Thrombolysed
Right pulmonary artery	7	4
Left pulmonary artery	14	9
Right ventricle	14	8
Right atrium	7	4

Thrombolytic agents tenecteplase (TNK), reteplase and streptokinase (STK)were used in the study. Thrombolysis with STK was used in two different regimens, One 2.5 Lakhs followed by 1 Lakh per hour for next 24 hours ,Second a two hour regimen of 7.5 lakh per hour. 56 patients were thrombolysed under the first STK regimen of 24 hours while 20 patients by the 2 hour regimen. TNK was used in 15 patients as thrombolytic agent while only in 5 patients reteplase was used . Classification of PE was done as massive , submassive and low risk (Table 4)

Table 4	Total	Thrombolysed
Massive	21	14
Submassive	105	72
Low risk	14	10

In patient of low risk PE only STK was used. In submassive and massive PE patients STK, TNK and reteplase all 3 thrombolytic agents were used .Table 4 depicts the number of patients in the respective group.

There were no major bleeding events defined as bleeding that required hospitalization or transfusion, was intracranial or into a body cavity, or was fatal during the study.

No other adverse events were reported during this study. At the first follow up visit after one month of tenecteplase therapy, all patients were clinically stable and there was no additional mortality.

DISCUSSION

The use of thrombolytics for the treatment of pulmonary embolism has remained controversial over several decades since the USFDA approval of streptokinase for acute pulmonary embolism in 1977 [31]. The clinical trials demonstrated early resolution of pulmonary embolism with all thrombolytic agents, the best thrombolytic agent still remains a dilemma for the doctor.

Thrombolytics are often used to dissolve or reduce the size of the thromboembolism and improve haemo-dynamic status and gas exchange. These agents are plasminogen activators which yield the fibrinolytic enzyme plasmin. Free plasmin is rapidly neutralised by the serine proteinase inhibitor alpha-antiplasmin. Fibrin bound plasmin is protected from this rapid neutralisation and clot lysis is promoted.

In spite of improved prevention and treatment of pulmonary embolism, the mortality is still estimated to be between 20 - 30%. It is the third most common cardiovascular cause of death, with two thirds of the deaths occuring within the first few hours as a result of severe haemodynamic and respiratory disturbances.[32,33,34]

Both streptokinase as well as urokinase have shown greater mortality in various studies possibly due to the serious bleeding complications associated with them [31]. On the similar lines, even alteplase has been documented to be associated with increased bleeding risk and 2.2% incidence of fatal hemorrhage including intracranial hemorrhage [35].

Alteplase, as a two hour infusion, is approved in the United States of America by the Food and Drug Administration for use in the treatment of pulmonary embolism and has been used in several studies. Prior to the use of thrombolytic therapy it is recommended that the diagnosis should be confirmed and contraindications are excluded as the side-effect of haemorrhage can be severe and fatal.

Tenecteplase is an alteplase molecule with three point substitution that increases its half life, increases the resistance to plasminogen activator inhibitor-I (PAI-1) by 200 folds and decreases the clearance by eightfolds. These properties offer great therapeutic convenience in thrombolysis allowing a single weight-adjusted bolus dose of tenecteplase as against the older thrombolytics. It also has greater fibrin specificity which has been reflected in reduced bleeding rates in ASSENT 2 trial [36, 37].

Reteplase is the first clinically available modified tissue plasminogen activator produced by recombinant DNA technology. It has a longer half-life (e.g. 13 - 16 minutes) than alteplase, making it suitable for a more convenient, double bolus administration compared with an infusion.[38] Reteplase was developed for the treatment of acute myocardial infarction and the recommended dose is 10 U followed by a further 10 U after 30 minutes. Each injection must be given over a period of no longer than 2 minutes.[39,38] In pulmonary embolism there is no significant difference in effect when the thrombolytic drug is injected through a peripheral vein or directly into the pulmonary artery,[41] and there is a less severe systemic fibrinogen depletion (a significant problem with streptokinase and urokinase).[39] Reteplase is also not as antigenic as streptokinase or urokinase, although anaphylaxis has been reported.[38]

The agent of choice, dosage may depend upon the clinical scenario and doctor persepective .

CONCLUSION

In our study, we reviewed the efficacy of various thrombolytic agents used and their associated complications associated with them did not show any significant discrepancies . The two hour regimen of streptokinase which was used in 4 patients showed to be quite effective as well . Because of the high cost and serious bleeding complications that may arise with thrombolytic therapy, thrombolytic treatment should be reserved for patients with massive PE complicated by severe haemodynamic compromise.

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