ABSTRACT

Background: Pulmonary embolism (PE) is a common clinical disorder which is associated with high morbidity and mortality if untreated. Due to the high morbidity and mortality associated with undiagnosed and poorly treated PE, there is a need for protocols based on risk factor assessment to facilitate early diagnosis of PE and protocols to ensure early and adequate treatment. The aim of this review is to highlight the risk factors associated with PE and discuss the modalities for optimal management of PE.

Method: Literature was reviewed using available medical journals, Science direct, Medline and Embase databases. Key words employed were: pulmonary embolism, deep venous thrombosis (DVT), venous thromboembolism (VTE) and thrombophilia. Information was also sourced from the British Thoracic Society and The National Heart, Lung and Blood Institute websites.

Results: Studies have shown that hypercoagulability state, stasis and local trauma to the vessel wall predisposes to PE. These studies further underscored that heparin is the cornerstone of therapy hence optimal diagnostic approach should be observed to avoid unnecessary anticoagulant therapy considering the fact that it carries a risk for bleeding.

Conclusion: This review was able to highlight the risk factors and management of pulmonary embolism. Patients with one or more predisposing factors and having high index of suspicion based on clinical assessment should be managed according to an agreed hospital protocol.

KEY WORDS: Pulmonary embolism, deep vein thrombosis, venous thromboembolism, thrombophilia

INTRODUCTION:

Pulmonary embolism is a potentially serious disorder which despite substantial advances, mortality and recurrence rate remains high. It often results due to proximal extension of a thrombus from the lower extremities to the pulmonary arteries with potentially serious consequences. Although the term PE encompasses embolism from many sources, including air, amniotic fluid, bone marrow, neoplastic, talc, and sepsis, this review intends to discuss the venous thromboembolic aspect of it.

In a large community study, PE had an overall annual incidence of 60-70 cases/100,000. Out of this figure, 50% developed VTE in hospital or institutional care, 25% were idiopathic cases and the remaining 25% were those with recognized risk factors. It accounts for 1% of all acute hospital admissions and unlike DVT, if left untreated, has a significant risk of fatality.

However, due to paucity of literature on PE from our local environment, there are no established national epidemiology figures on PE except from some local studies carried out in some centres. Awotedu AA et al, reported on post-mortem and ante-mortem of 60 patients with fatal PE in UCH Ibadan, with average age of 47 years between 1985 and 1989. The report showed that PE occurred in 3.8 percent of all autopsied patients, with a male to female ratio of 1.4 to 1.

Igun GO, in a 10-year review of 42 clinically diagnosed venous thrombo-embolisms in Jos with average age of 41 years, revealed that the male to female ratio of PE was 2.5 to 1.

Recurrence of PE, though non-fatal, is often seen in the first one to three years especially in patients with reduced mobility leading to hypercoagulability state as a result of a disease.
Risk factors of PE may include orthopaedic surgery, oestrogen therapy, long-haul flights, obesity, pregnancy/puerperium and many more factors. Increasing age, though unclear as it is an independent risk factor, is also associated with exponential increase in risk of VTE.

In PE, over-diagnosis is as likely as under-diagnosis; it is generally over-diagnosed and confirmed in less than one third of clinically suspected cases. This is confounded by a clinical picture that may be subtle, atypical or obscured by another coexisting disease.

**RISK FACTORS:**

In addition to genetic predisposition, identification of other risk factors such as conditions that results in immobility or hypercoagulability state is very vital in PE patients. Studies have shown a direct relationship between increasing age and VTE. Although cigarette smoking was strongly associated with PE in the past, this has not been proven or confirmed in recent times. Other risk factors for VTE could be classified as follows:

i. Surgery: Predispose patients to PE and this is especially common with pelvic, abdominal and orthopaedic types. Khan A et al established that use of prophylaxis has a substantial reduction in the incidence of post-operative VTE.

ii. Obstetrics: this occurs irrespective of the trimester but is commonly seen in the postpartum period. In three large studies conducted separately it showed PE in 1-2 of 7000 pregnancies, less than previously supposed; majority of the cases occurred post-partum, particularly with pre-eclampsia, caesarean section, and multiple births.

iii. Thrombophilia, a tendency to increased clotting, is often seen in 25-50% of patients with VTE. However, some acquired risk factors must be present (e.g. pregnancy) for thrombosis to occur in these patients.

iv. Oestrogen therapy: this increases the risk of PE either in the form of oral contraceptive pill (especially the third generation oral contraceptives) or hormone replacement therapy.

v. Malignancy: there is an increase risk of cancer being detected in some patients with idiopathic VTE. This is often by a combination of careful clinical review and comprehensive investigations and may sometimes take couple of months after the first episode.

vi. Immobility: some chronic debilitating conditions that lead to reduce mobility may result in hypercoagulability state thus increasing the risk of PE as seen in institutional care or hospitalisation due to congestive cardiac failure, COPD, neurological disability, thrombotic disorders or inflammatory bowel disease.

**CLINICAL PRESENTATION:**

PE can mimic or co-exist with other medical conditions thus a diagnostic puzzle. Patient may present in a subtle or classical way and this depends on the size, number and site of the thrombi/emboli and risk factor present.

Detailed history taking and physical examination forms the cornerstone in PE. Several studies have shown sudden dyspnoea to be the most frequent symptom of pulmonary embolism while tachypnoea and type 1 respiratory failure (?PaCO2, ?PaO2) forms the most frequent signs. In massive Pes, the presence of dyspnoea, syncope, and cyanosis usually supports the diagnosis whereas finding of pleuritic pain, cough, and haemoptysis often suggests a small subpleural embolism. Physical examination often reveals findings of right ventricular dysfunction which may include left parasternal heave, visible pulsatile neck veins with v-waves, a systolic murmur maximal at the left lower sternal border with inspiratory accentuation and a loud P2.

**INVESTIGATIONS:**

Investigations for suspected PE include basic laboratory investigations and some more specialised investigations like the plasma D-dimers, nuclear and radiological techniques. Thrombophilia (acquired or inherited) screening should be considered in those less than 50 years of age with positive family history of VTE and or recurrent PE.

i. Plasma D-dimers: this plays an important role in excluding PE notwithstanding the fact that raised levels are occasionally seen in obstetrics, hospitalised patients, malignancies, inflammatory diseases, peripheral vascular disease and with increasing age. The test has high sensitivity but poor specificity, hence it should only be considered following assessment of clinical probability. It should not be performed in those with
high clinical probability; negative test excludes VTE in those with low clinical suspicion.

ii. Nuclear medicine: Isotope lung scanning (ventilation perfusion scans) helps greatly in diagnosing PE. Although a normal scan reliably excludes PE, high probability scans have some false positives and is hence not diagnostic. Van Beek EJR et al showed that some false positives were found in those with previous rather than current Pe.

iii. Leg ultrasound: plays a role as an initial test in those with clinical DVT or in an attempt to reduce the need for lung imaging or if there is an inconclusive result from some investigations. It helps to preclude the need for further investigations if it was able to identify DVT. It has limited accuracy as it could fail to detect asymptomatic proximal DVT; thus a single normal scan should not be relied on for exclusion of PE. This is further supported by a study conducted by Daniel KR et al on patients with non-diagnostic isotope lung scans and a single negative leg ultrasound scan; they found that one third did have PE on pulmonary angiography.

iv. Conventional pulmonary angiography: a gold standard in diagnosis now has limited use because of its invasive nature and limited radiological experience. Its advantage over CTPA is that subsegmental clot is not likely to be missed.

v. Computed tomographic pulmonary angiography (CTPA): is increasingly gaining acceptance as a diagnostic tool in PE, it is thus recommended as the preferred initial imaging. It is clearly superior in specificity to ventilation perfusion scan and also helps in assessing clinical severity. In comparison with isotope scans it is easier and quicker to perform, rarely needs further imaging and helps provide the true alternative diagnosis when PE is excluded.

vi. Echocardiography: is diagnostic in massive PE and gives prognostic information. Its diagnostic accuracy is better with this approach especially in intracardiac and intrapulmonary thrombus.

vii. Transthoracic ultrasound is considered as an adjunct rather than an alternative to other imaging; it is not widely used.

viii. Helical thoracic CT scan with contrast: it has good sensitivity and specificity to the level of segmental arteries; however, the type of scanner and the competence of reporting vary.

ix. Doppler ultrasonography or venography: of leg veins, it is documented that 70% of patients have detectable DVT at time of presentation.

x. Chest radiograph may be normal or show pleural effusion, dilated pulmonary artery, oligaemia or linear atelectasis.

xi. Arterial blood gases are routinely analysed in PE. It shows type 1 failure (?PO2 ?PCO2).

xii. ECG may be normal or show sinus tachycardia, right bundle branch block, right ventricular strain, right axis deviation or atrial fibrillation.

TREATMENT:
Treatment of PE basically includes supportive therapy, thrombolysis, heparinisation and oral anticoagulation; however, the treatment may vary depending on the agreed hospital protocol. Figure 1 shows standard protocols employed in the management of PE at the Hammersmith hospitals trusts.

Supportive treatment basically includes oxygen therapy, analgesia with morphine in patients with painful distress. Plasma expanders and inotropic agents could be used in hypotensive cases.

- Anticoagulation: heparin forms the backbone of management. It accelerates the action of anti-thrombin III thus preventing additional thrombus from forming and also causes fibrinolysis of some clots present. Heparin is discontinued when the achievable target INR (2.0-3.0) is reached and patient maintained on warfarin. The use of low molecular weight heparin (LMWH) confers additional benefit as compared to unfractionated heparin (UFH) in terms of side effects and dosing hence most patients could now be managed without hospitalisation; this is notwithstanding the fact that it has to be given parenterally. Studies on Ximelagatran, a direct thrombin inhibitor taken orally, is yielding positive results on PE patients; other studies on this further supports it to be safe and effective as the other LMWH in VTE. Simonneau G et al showed that use of LMWH in PE is effective as UFH in those with DVT. There is
argument as regards to duration of treatment with warfarin in PE. The general consensus is that treatment should be for a period of 3 months for a first episode of idiopathic PE. PE patients with persisting risk factors should go on indefinite anticoagulation notwithstanding the fact that there is increase risk of bleeding with no change in mortality. In some special situations like pregnancy warfarin should be avoided (because of its teratogenic effect) until after delivery; alternatively, therapeutic doses of LMWH should be used. At term UFH should be substituted because its anticoagulant effect can easily be reversed when the need arises. However, anticoagulation should continue for either 6 weeks or 3 months depending on the situation on ground.

- **Thrombolysis:** it is recommended to be the first line of treatment in patients with massive PE who are haemodynamically unstable; studies have shown significant reduction in mortality in those patients. In non-massive PE, the risks of thrombolysis have outweighed the benefits as there is an increase risk of major haemorrhage, thus it shouldn't be used as a first line treatment. The drugs employed in order of preference include alteplase, Streptokinase and urokinase. Although expensive, alteplase has an advantage because it is readily available and doesn't worsen hypotension.

- **Embolectomy:** surgical Embolectomy and or mechanical technique are often reserved when thrombolysis failed or is absolutely contraindicated in a critically ill patient. In mechanical technique, large emboli are fragmented via right heart catheter.

- **Inferior vena caval filters:** this is an invasive procedure and should be considered where facilities and expertise are readily available. Its use is less favoured in modern practice and employed only where anticoagulation is contraindicated or failed to prevent recurrence of PE as in malignancies or continuing DVT.

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**Hammersmith Hospitals Trust Protocols**

- PE suspected: collapse or hypotension?
  - Present or Inminent: No, patient stable
  - Urgent echocardiogram or spiral CT or VQ, whichever can be done soonest
  - PE confirmed: Non-diagnostic: PE excluded: Non-diagnostic: High probability
    - Spiral CT with contrast, "CT pulmonary angiogram" protocol or echocardiogram
    - Seek other diagnosis
    - Leg ultrasound
    - Treat
  - Other result: Proximal DVT
    - Specialist advice
    - Anticoagulation

**Figure 1:** showing the Hammersmith hospitals trusts protocol employed in the management of PE.
CONCLUSION:
The review shows that pulmonary embolism is a potentially serious disorder which despite substantial advances in diagnosis and treatment still has high mortality and recurrence rates. Early and accurate diagnosis is a very important step in reducing the morbidity and mortality associated with PE as it allows for early commencement of appropriate treatment. This will ensure a reduction of under-diagnosis as well over-diagnosis, a situation which is aided by a clinical picture that may be subtle, atypical or obscured by another coexisting disease, thus avoiding unnecessary anticoagulant therapy and its associated risk for bleeding. Clinical assessment is important in documenting the clinical probability of PE especially in those with predisposing factors and high index of suspicion. In addition to imaging, D-dimer assay where available should be carried out except in those with high clinical probability. Appropriate treatment which usually consists of supportive therapy, thrombolysis, heparinisation and oral anticoagulation should be commenced early. The use of properly structured PE management hospital based protocols is strongly advocated as this would go a long way in achieving early diagnosis and appropriate treatment, as well as avoiding misdiagnosis.

REFERENCES:


