

Review Article

Pulmonary Embolism, Venous Thrombo-Embolism and Deep Vein Thrombosis associated with Hip Fracture in Elderly: A Critical Review on Diagnosis and Prevention

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Abstract:

Deep Vein Thrombosis (DVT) of lower extremity and subsequent Venous Thrombo Embolism (VTE) often leads to Pulmonary Thrombo Embolism (PTE) otherwise called Pulmonary Embolism (PE). This review paper explores different international guidelines and various studies to discuss presentations of these three entities associated with hip fracture in elderly and ways to establish their presence with aim to prevent them.

DVT, VTE, PE are consequences of hip fracture often suffered by elderly people who are prone to fall while attempting to walk. DVT may often be asymptomatic and PE may often present with occult signs and symptoms. As such both DVT and PE may often be missed by unsuspecting clinician. Patient undergoing hip fracture surgery (HFS) with untreated asymptomatic preoperative DVT or occult PE may suffer from severe PE resulting in shock and death. Elderly patient undergoing HFS may develop post-operative DVT and PE if proper prophylactic measures are not taken both before and after surgery. DVT can be diagnosed by D-dimer test and ultrasonography (USG). Multi Detector CT venography is more confirmatory than USG. However negative D-dimer test means absent DVT. CT Pulmonary Angiography (CTPA) is an effective diagnostic tool for PE.

For prevention of DVT and VTE, pharmacological prophylaxis with low molecular weight heparin e.g. Enoxaparin is the drug of choice. For mechanical prophylaxis Intermittent Pneumatic Compression (IPC) device is the choice for the clinician provided USG shows no evidence of DVT in the lower extremity. In case of USG positive DVT, mechanical prophylaxis is contraindicated.

Key Words: Deep Vein Thrombosis, Hip fracture, Pulmonary Embolism, Venous Thrombo Embolism.

Introduction

Pulmonary Embolism (PE) or Pulmonary Thrombo Embolism (PTE) is caused by blockage of a pulmonary artery usually by a blood clot from Deep Vein Thrombosis (DVT) formed in the lower extremity commonly observed in association with hip fracture in the elderly population. DVTs are at risk of dislodging and migrating to lung circulation. These conditions are generally regarded as a continuum known as Venous Thrombo Embolism (VTE). This review deals with presentations of PE, VTE & DVT observed before planning surgery for fracture of hip along with various methods of diagnosis and different modalities of preventive strategies advocated in different studies and guidelines. Femoral neck fractures are a common health problem in the elderly population. Over 300000 hip fracture cases occur annually in the United States alone, with even higher global numbers¹.

PE, VTE and DVT: Paradigm of presentations

PE is characterized by three classic symptoms e.g. shortness of breath, chest pain, and coughing up blood. Normally

pulmonary artery, bronchial artery, and intra alveolar gas diffusion supply lung with oxygen. Less than 15% of patients experience deficit in all three oxygen sources simultaneously².

PE can be classified into three categories based on the degree of danger: high-risk, intermediate-risk, and low-risk. High-risk individuals have hemodynamic instability, manifested by hypotension and shock. They are prone to sudden death. Moderate risk individuals are hemodynamically stable. They can present with right heart dysfunction or myocardial cell impairment. In the acute phase, 3–15% of moderate risk patients may experience deterioration or even succumb to death. Low-risk individuals usually do not display the above symptoms³.

In some instances, patients with PE may exhibit no manifestations or experience mild and transient symptoms. This can easily lead to missed diagnosis and often misdiagnosis. We call it occult pulmonary embolism (OPE)⁴. Patients with mild symptoms may present as other illnesses and may not receive an early diagnosis of PE. In one study 33.5% such patients received delayed diagnosis for PE⁵.

Undiagnosed and untreated, OPE can lead to pulmonary artery thrombosis organization and remodelling of pulmonary vessels, leading to vascular stenosis or occlusion and which can cause pulmonary arterial hypertension⁶. Additionally, OPE can precede more severe embolisms thereby increasing the risk of recurrence and can increase the potential for fatal embolism⁷.

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Research indicates that the occurrence of OPE is more common in patients with proximal DVT (which involves popliteal vein thrombosis and femoral vein thrombosis) compared to those with distal DVT (calf muscle venous plexus thrombosis)⁸. Distal DVT may sometimes be asymptomatic but with its proximal extension to proximal veins and pulmonary arteries, it can eventually produce severe symptoms or even cause death⁹.

Development of symptoms of VTE is dependent on the extent of thrombosis, perfusion by collateral vessels, and severity of occlusion of the associated vessel¹⁰. Most cases of VTE begin as DVT in the calf veins, progresses to proximal veins, and finally advance to PE¹¹.

Thrombus in the popliteal vein or a vein proximal to the popliteal vein is called proximal DVT. Thrombus in the tibial, peroneal, soleus, or gastrocnemius vein is called distal DVT¹².

According to Protty et al DVTs in their study occurred mostly on the ipsilateral side of the hip fracture. A similar study has shown a tendency for DVTs to occur on the same side as the hip fracture. This phenomenon suggests local vessel injury and usually immobility of affected limb may be a more important factor than general hypercoagulability in causing DVT after hip fracture¹³.

Isolated calf muscular venous thrombosis (ICMVT) is a unique phenomenon and is confined to the gastrocnemius and soleal veins. It accounts for 5.6 to 31.3% of DVT in lower extremities¹⁴.

Investigations have shown that more than one-third of patients with DVT are confirmed to have PE and in many such patients the PE may be asymptomatic¹⁵. One important issue to remember is that DVT occurs in 62% of older patients with hip fracture who undergo a delayed operation (> 48 h after injury)¹⁶.

VTE may sometimes present without symptoms but in cases of symptomatic DVT, patients may experience leg pain, swelling, and local erythema. Shortness of breath, chest tightness, or shock may be observed in patients with PE as a consequence of VTE¹⁷.

Hip fracture is always a major risk factor for VTE, and its correlation has been known for more than half a century¹⁸. It is also an age-related problem with a substantial long-term decreased survival resulting from vascular deaths¹⁹.

General risk factors for VTE include advanced age, cancer, prior VTE, venous insufficiency, pregnancy, trauma, frailty, and immobility. However lower limb fractures and surgeries are known higher risk factors for the development of DVT and PE²⁰⁻²¹.

Typical osteoporotic hip fractures caused by low-energy fall injuries, commonly occur in older patients. DVT usually occurs any time after HF in these patients, and the hypercoagulability of blood normally increases the risk of DVT. The period of DVT formation is relatively short, and blood clot formation can occur at any time, in older patients²².

Patients with proximal HF may present with high risk of

thromboembolic complications. Orthopaedic injury, combined with patients' advanced age, medical comorbidity and poor postoperative mobilization, contribute to the high risk of VTE. According to several studies patients undergoing surgery for hip fractures are commonly known to be at high risk for VTE, with relative high rates of DVT and PE²³⁻²⁴.

According to one study there are five independent predictive factors observed for preoperative asymptomatic PE in patients of aged ≥ 60 years with hip fracture. They are: hypertension, cerebrovascular accident, smoking, and two raised biomarkers (high potassium and D-Dimers)²⁵.

Currently, the prompt identification of PE can be easily neglected or misdiagnosed because of its nonspecific symptoms and variable levels of severity in many clinical situations. Relying solely on clinical symptoms for diagnosis is not justifiable and still needs imaging equipment. Asymptomatic individuals often have overlooked the diagnosis of PE by refusing further examinations. Researchers have discovered that 72% of asymptomatic DVT patients often develop OPE. These OPEs are diagnosed after undergoing CT pulmonary angiography (CTPA) testing and 32–72% of patients with DVT experience covert PE according to one study²⁶.

According to Atzmon et al, a history of preoperative PE emerged as a significant risk factor for postoperative PE and there is no significant correlation between surgery type and PE incidence. This study underscores the mortality risk associated with preoperative PE in femoral neck fracture patients. It stresses the need for vigilant PE risk assessment and management. This study's crucial finding was that over a 5-year period, the mortality rate for patients who experienced preoperative PE was 87.1%, compared to 59.7% for patients without PE. It highlights the heightened mortality risk for patients with a preoperative history of PE following proximal femoral fracture, presenting a 37-fold increased risk for postoperative PE²⁷.

One literature indicates that, irrespective of the treatment received, 1-year mortality rate following a HF ranges between 14% and 58%²⁸. Among the elderly aged 65 years and older, this mortality increases by an additional 4% annually²⁹. As most patients with HF tend to be in the elderly age-group which is vulnerable to perioperative complications, the relative risk of VTE in patients with HF is always higher than in these patients with fractures at other sites³⁰.

Researchers have agreed, there is a risk of progression of PE during and after operation if preoperative PE is missed and not treated in time. Hence, prevention and diagnosis of preoperative PE is very important for patients with HF who undergo delayed surgery and more active screening is helpful in such cases¹⁸.

Cong et al did a study to investigate DVT formation in HF using daily doppler ultrasonography, and determined the occurrence of DVT over time through survival analysis. Their findings were as follows: (a) 148/331 (44.7%) patients had diagnosis of preoperative DVT and among them 93.9% of DVT were peripheral. (b) DVT mainly occurred in the first 3

days of admission predominantly from admission to day 1, and DVT formation was stabilized from day 5 onward. (c) Age, fracture type, Hemoglobin (Hgb) and Hematocrit (Hct) levels affected the dynamic occurrence of preoperative DVT. (d) Hct level was found to be independent predictor of DVT survival. With other factors being constant, their study showed that patients with Hct <40% had a 2.079-fold incidence of the risk of preoperative DVT than those with Hct \geq 40%²².

According to one study the incidence of preoperative DVT in patients with HF is between 6–62%³². It has been observed that the high prevalence of multiple comorbidities makes older patients more susceptible to DVT than younger patients³¹. Preoperative DVT is also known to occur in 9% to 62% of patients in spite of receiving prophylaxis¹⁶.

Zuo et al reported that 20.1% of 578 patients with intertrochanteric fracture had DVT upon admission and the risk of DVT gradually increased with time after injury. Their study also showed that every delay of one day from admission was associated with a 37% increased risk of DVT³³. Another study claims that in patients with intertrochanteric fracture, 39.1% had preoperative DVT³².

Shin et al studied risk factors for VTE in HF patients with a delay of more than 24 hours from injury to surgery. The authors claimed that female gender, subtrochanteric fracture, pulmonary disease, cancer, previous hospitalization for VTE, and varicose veins are important risk factors for VTE³⁴.

Studies have shown that patients with HF have a high risk for VTE events because of endothelial injury of adjacent blood vessels, hypercoagulability following coagulation cascade, and venous stasis resulting from immobilization³⁵.

According to one study, incidence of preoperative DVT in patients who underwent surgery >48 h after fracture was higher than that in patients who underwent surgery within 48 h of sustaining the fracture³⁶. Even surgery for proximal femur fractures 48 h after an injury is a risk factor for developing post-operative VTE and proximal DVT³⁷. Prevalence of preoperative VTE as high as 29.8% has been reported in one study for patients with hip fracture, and as such preoperative assessment for VTE is recommended for patients with surgical delay over 24 hours²².

Research indicates that the occurrence of OPE is more common in patients with proximal deep vein thrombosis (including popliteal vein thrombosis) compared to those with distal deep vein thrombosis (calf muscle venous plexus thrombosis)⁷. This could be due to the proximal vein's increased thickness, leading to larger blood clots and a greater likelihood of a dislodged embolus blocking the pulmonary artery. Researchers have found that 72% of asymptomatic DVT patients are to have developed OPE detected only after undergoing computed CT pulmonary angiography (CTPA) testing¹⁵.

McNamara et al demonstrated that intertrochanteric fractures were a risk factor for symptomatic VTE, and incidence of VTE from intertrochanteric fracture was twice as high as that of intracapsular HF³⁸.

Anemia if present in older patients, has been demonstrated to increase the risk of DVT³⁹. Cancer patients who sustain fractures are at an increased risk of DVT and close monitoring and active intervention are required in these patients to prevent venous thrombosis⁴⁰. Lee et al reported the incidence of DVT after major lower limb orthopedic surgery and found a 5-fold increased risk of DVT in patients of 50–69 years. A 10-fold higher risk of DVT in those age > 70 years then in those aged < 49 years were also observed⁴¹.

D-Dimer, Ultrasonography and CTPA: Why and When

D-dimer is a highly sensitive marker for PE. Research shows that elevated D-dimer levels within 24 hour of admission are an independent marker for OPE. As such D-dimer can act as a vital indicator for pulmonary embolism²⁵.

D-dimer is a clinically relevant biomarker of activation of hemostasis and fibrinolysis. It is a relatively sensitive marker of DVT useful for patients with fracture before and after surgical operation. In addition to HF, high levels of D-dimer are also frequently found in patients with infection, and other medical conditions such as heart failure and renal failure, cases of liver disease, inflammation, malignant tumor, pregnancy, trauma, and even after recent surgery. One important aspect of D-dimer test is that a negative result usually means the absence of DVT. Older patients with a hip fracture may show elevated levels of D-dimer due to their underlying diseases and trauma regardless of VTE. Therefore there are limitations to singular use of the D-dimer test for confirming the presence of DVT. This is because many confounding factors are associated with D-dimer elevation, including trauma, female gender, increasing age, immobility, and drug use^{18,42-43}. Different studies claim that only a negative D-dimer result combined with a low level Wells score (-2 to 0) can safely rule out VTE⁴⁴.

Soluble fibrin is a more sensitive marker of DVT than D-Dimer. Several researchers have shown high plasma levels of soluble fibrin in the early stages of thrombotic diseases⁴⁵. In addition to D-dimer, high level of fibrinogen was also recognized as one of the well-established risk factors for VTE. It is hypothesized that the elevated fibrinogen increases fibrin network density, blood viscosity, and the resistance of clots to fibrinolysis, thereby leading to a hyper coagulable state⁴⁶. According to one author the elevated levels of D-dimer and fibrinogen, coexisting movement disorder, and multiple fractures, as well as bed rest for more than 7 days, were identified as risk factors of VTE⁴⁷.

Ultrasonography (USG) is the first-line imaging test and preferred approach for diagnosing DVT particularly in the proximal portion of leg veins. USG is non-invasive, can be performed immediately and can easily be used as a component of follow-up exams. However, according to a recent meta-analysis, USG showed a sensitivity of 94.2% and a specificity of 93.8% in DVT of femoral vein and popliteal vein, whereas it revealed a relatively low sensitivity at 67.0% in below knee DVT in the distal vein⁴⁸.

In study of Roberts et al incidence of DVT may increase to as high as 62% in HF when the time to surgery was delayed by

more than 2 days. In this study, some patients converted from a negative to a positive result owing to daily performed USG, resulting in a higher incidence rate (44.7%) than in those with only one USG⁴⁹.

In current clinical practice, D-dimer and Doppler imaging are the mainstream investigations for diagnosis of VTE. However, the VTE may not be recognized in older patients due to atypical presentation³⁰.

CT venography has emerged an alternative method of USG because it ensures short examination time and has high sensitivity and specificity at 100% and 96.6%, respectively⁵⁰.

In recent years, high-resolution indirect MD (Multi Detector) CT venography has enabled more accurate and prompt diagnosis of VTE, and has been acknowledged as a useful technique for evaluating VTE in hip fracture patients. Indirect MDCT venography can detect both DVT and PE with relative easier screening process with no change in patients' positioning and by obtaining combined images of lower extremity venography and pulmonary angiography⁵¹.

VTE may occur after a fracture and it also may exist as asymptomatic underlying condition. This form of VTE may progress to fatal complications like intra or postoperative fatal PE. Considering hip fracture-induced bed rest and age related risk factors, more active screening test like MDCT venography is needed to diagnose preoperative VTE after hip fracture and it seems to be the most effective imaging option⁴⁴.

According to one text book, distal DVT is generally believed to have a lower likelihood of causing PE, but there is no agreement on how it should be treated⁵².

The latest American College of Chest Physicians (ACCP) guidelines recommend serial imaging of the deep veins for 2 weeks instead of anticoagulation in patients with isolated distal DVT without severe symptoms or risk factors for thrombosis extension. The guidelines in addition consider ICMVT is associated with a lower risk of extension than that of calf axial vein thrombosis⁵³.

CT Pulmonary Angiography (CTPA) is an effective diagnostic tool for detecting PE. However, its application is restricted by its risk of radiation exposure, probable adverse reactions to contrast agents and high cost limiting its widespread clinical utility⁵⁴.

For patients aged ≥ 60 years with HF for whom surgery is delayed, because of the high incidence of preoperative asymptomatic PE and the inferior prognosis in individuals with PE, routine CTPA examination for preoperative asymptomatic PE could be useful²⁵.

High-risk patients with PE often do not have the physical condition to undergo CTPA and during transportation of these patients, the displacement of large emboli can easily lead to sudden death. Ultrasound echo cardiography can be performed beside the bed as an alternative procedure to assist in diagnosis in these patients⁵⁵.

Prophylaxis of VTE: Preventing DVT and PE

Measures are required before surgery for patients who sustain fractures around the hip to reduce the incidence of and for

management of preoperative VTE. After individualized risk assessment, according to current guidelines both pharmacological and mechanical VTE prophylaxis are recommended⁵⁶. Various thrombo prophylactic modalities have been recommended by several guidelines, including the American Academy of Orthopaedic Surgeons (AAOS), the American College of Chest Physicians (ACCP), and National Institute for Health and Clinical Excellence (NICE)⁵⁷.

According to one observation, without thrombo prophylaxis following a hip fracture, the incidences of VTE, proximal thromboembolism, and fatal PE range between 42-50%, 20-27%, and 0.6- 7.5%, respectively³⁴. In patients without therapeutic anticoagulation, a significant number of patients acquired isolated distal DVT which progressed to proximal DVT⁵⁸. Even with anticoagulation therapy, a longer time before surgery has been reported as a relevant factor for formation of DVT⁵⁹.

According to Xia et al who observed that preoperative therapeutic anticoagulation for ICMVT may not effectively decrease the risk of thrombus progression. Accordingly direct surgery for femoral neck fracture regardless of the status of ICMVT seems appropriate⁴⁷.

Low Molecular Weight Heparin (LMWH) has become the standard pharmacological agent according to many guidelines based on increased bio availability, low bleeding complications, and short plasma half-life⁶⁰.

Enoxaparin is one of the most widely used LMWHs and it is injected subcutaneously once daily at a dose of 4,000 IU immediately after injury to 12 hours before surgery. For preoperative VTE enoxaparin is injected subcutaneously twice daily at a dose of 100 IU/kg regardless of symptoms. Prevention of postoperative VTE can be done with the same methods applied to patients undergoing ordinary hip surgery. Active pharmacological prophylaxis is required immediately after injury in patients with HF but there are limitations in the choice of administered anticoagulants because undergoing surgery within the earliest possible time also needs to be considered at the same time¹⁸.

Preoperative pharmacological prophylaxis is always recommended in cases where surgical delay is expected. It is begun as early as within 14 hours of admission, following assessment of risk for bleeding and thrombosis. Postoperative pharmacological thrombo prophylaxis beginning 12 hours after wound closure, and continuing for at least 28 days is recommended⁶¹.

As mentioned earlier, like hip fracture alone, post hip fracture surgery (HFS) also causes DVT, VTE and PE. Without any thrombo prophylaxis, the risk of developing DVT following HFS is over 50% and that of developing PE is 7%-11%⁶².

According to Machlus et al recent use of anti-platelet drug and prophylactic anti coagulation are considered as protective factors for VTE in HF cases⁴⁶.

Mechanical prophylaxis aims to prevent venous congestion thereby prevents DVT. It includes compression stockings, elastic bandages, foot pumps, and intermittent pneumatic

compression (IPC) devices etc. Of these, foot pumps and IPC devices are preferable considering patient compliance and preventive effects. The biggest advantages of mechanical prophylaxis is that there is no risk of bleeding and it is applicable without specific treatment from the preoperative period. When bleeding is detected or pharmacological prophylaxis is constrained it is still usable⁶³.

Only contraindication to mechanical prophylaxis is positive evidence of DVT and it must be excluded before institution of mechanical prophylaxis. If there are no contraindications, application of compression stockings or IPC is recommended on admission and post operatively until mobilization close to the patient's pre admission status can be achieved⁶³.

In case of preoperative positive DVT cases, fatal PE can be avoided by insertion of retrieval inferior vena cava (IVC) filters in selected cases (e.g., those for whom pharmacological treatment for thrombus removal cannot be sustained for a sufficient length of time until surgical intervention or anticoagulation is not applicable). IVC filters should also be used for patients with history of recurrent PE despite sufficient use of anticoagulants or with patients who has contraindication to anticoagulants⁶⁴.

Conclusion

Elderly population in general are susceptible to suffer from fall resulting in HF. One big challenge in HF management is preoperative occurrence of DVT, VTE and subsequently PE. DVT and VTE before surgery may also lead to peri-operative and post-operative PE. USG of lower extremity, D-Dimer, MD CT venography (if available) and CTPA should be done selectively or in combination before HF surgery. Proximal DVT of lower extremity and hip surgery after 48 hours of injury are important risk factors for pre or post-operative PE. Asymptomatic as well as symptomatic DVT must be managed with LMWH until surgery and LMWH should be continued following surgery for at least 28 days. Occult PE if missed may cause fatal post-operative PE. If DVT is negative on USG, IPC devices are useful preventive measures to prevent VTE and PE before and as well as after surgery. This mechanical device should also be used on post hip surgery patient until full mobilization is achieved.

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