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Original Research Paper

Surgery

DEEP VEIN THROMBOSIS – A SYSTEMATIC REVIEW

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ABSTRACT Deep vein thrombosis (DVT) is the formation of blood clots in deep veins, commonly the leg veins and the pelvic veins. DVT is a potentially fatal condition leading to increased mortality and morbidity if not diagnosed and treated promptly.Incidence is more prevalent in 60- 65 years of age because of increased pro-coagulant factors like factor VIII, factor VII, homocysteine, fibrinogen. With the increase in age the risk of DVT development increases exponentially.All bed ridden patients should receive sequential compression device therapy as primary DVT prophylaxis in the form of intermittent pneumatic compression device (IPCDs), graduated compression stocking (GCS), and the venous foot pump.The pharmacological agents used in the prophylaxis of DVT include low-molecular-weight heparins (LMWH), fondaparinux, Unfractionated heparin (UFH), new oral direct selective thrombin inhibitors and factor Xa inhibitors.The complications of DVT include development of Pulmonary embolism (PE) , Paradoxical emboli, Recurrent DVT, Post thrombotic syndrome. Approximately 4% individuals treated for DVT develop PE. It accounts for 10-12% mortality rate in hospitalized patients.The prevention and treatment must be upgraded continuously with evidence base strategies. This article aims at reviewing the clinical presentation, diagnostic and treatment modalities of DVT.

KEYWORDS : deep vein thrombosis, treatment of DVT, DVT prophylaxis, complications of DVT, surgery and DVT.

INTRODUCTION

Deep vein thrombosis (DVT) is the formation of blood clots in deep veins, commonly the leg veins and the pelvic veins. DVT is a potentially fatal condition leading to increased mortality and morbidity if not diagnosed and treated promptly. The risk of developing DVT is inherently higher in patients undergoing long surgeries. Pulmonary embolism(PE) is an acute dreaded complication of DVT [1]. The incidence of DVT is 1 in 1000 people annually [2]. The hospitalization rate for DVT and PE has been increasing.The prevention and treatment must be upgraded continuously with evidence base strategies. This article aims at reviewing the clinical presentation, diagnostic and treatment modalities of DVT.

About 50 articles were identified regarding DVT andits risk factors, clinical approach, prophylaxis and treatment from MEDLINE, EMBASE, Cochrane library database and google search (from 2000 to 2021). Of those, we narrowed to nearly 10 articles and collected data and with reference to various guidelines we made this review article on deep vein thrombosis in surgery.

RESULTS:

Risk Factors

Incidence is more prevalent in 60- 65 years of age because of increased pro-coagulant factors like factor VIII, factor VII, homocysteine, fibrinogen. With the increase in age the risk of DVT development increases exponentially. The incidence of DVT per 1000 person-years increases with age[3] . Elevation of D-Dimer and atherosclerotic disease favor development of DVT [4] . Prevalence of DVT is more common among males than females. However, in the third decade of life it is more common in females than in males due to excessive estrogen levels [3]. Hormones: Oral contraceptive pills, Nuva ring, Depo provera injection, testosterone supplementation contribute in the formation of thrombosis [3]. In a German cohort study, women presented more often, women with higher sex hormone levels are at high risk for thrombophilia. Major surgery like total hip replacement, total knee replacement, laparotomy, bowel resection, colectomy, cholecystectomy, emergency general surgery, gastrointestinal ulcers surgery, appendicectomy [5]and surgeries including prolonged immobilization contribute a major risk factor for the development of deep vein thrombosis (Gantz et al., 2020). As the age increases cancer and its treatment, immobility, stroke paralysis predisposes VTE.

Obesity remains an independent risk factor for the development of DVT, BMI ≥ 30 has 2-3 fold increased risk for DVT with increasing BMI the risk increases further [6-8]. Trauma / Fractures of lower limb which restrain the patient from mobilization increases the risk for DVT [3]. Varicose veins/ Superficial thrombophlebitis predispose DVT development due to venous stasis. During Pregnancy the chances of DVT occurrence increases as venous stasis is more prevalent in pregnancy due to pelvic vein compression of gravid uterus [3]. Venous catheterization is also a risk factor for DVT.

Genetic factors include heterozygous prothrombin gene mutation, heterozygous factor V leiden mutation, homozygous prothrombin gene mutation, homozygous factor V leiden gene mutation and anti-thrombin deficiency [3,9-11]. Anti thrombin deficiency is one of the potent inherited risk factor for DVT [3,12]. In pediatric age group, the triggering factors for development of thromboembolism are insertion of central venous lines, cancer, and chemotherapy. Severe infection, sickle cell disease, trauma, and antiphospholipid syndromes are clinical conditions associated with hypercoagulability states [13]. A strong association between recent respiratory infection and VTE has been described by Clayton et al[14].

Prophylaxis Of Dvt

All bed ridden patients should receive sequential compression device therapy as primary DVT prophylaxis in the form of intermittent pneumatic compression device (IPCDs), graduated compression stocking (GCS), and the venous foot pump. These devices prevent venous stasis and enhances blood flow in the deep veins and prevent the development of venous thrombosis [16].

ASH guidelines recommend assessment of risk of bleeding and thrombosis and suggest use of mechanical prophylaxis with Intermittent Pneumatic Compression Devices (IPCDs) alone in patients with high risk of bleeding and combined

mechanical and pharmacological prophylaxis in patients at high risk for VT [17].

Gould et al says the risk of VTE after surgery remains for at least 12 weeks [18]. Sweetland et al quotes that in a population based study the risk for VTE remained 10- 50 times higher in weeks 7 to 12 after surgery [19]. Short-term prophylaxis is less than 2 weeks and extended prophylaxis is for 3-6 weeks.

The pharmacological agents used in the prophylaxis of DVT include low-molecular-weight heparins (LMWH), fondaparinux, Unfractionated heparin (UFH), new oral direct selective thrombin inhibitors and factor Xa inhibitors. Studies have shown that the incidence of DVT, PE has been reduced by low dose UFH [20].

Fondaparinux, an indirect selective inhibitor of factor Xa has been approved for prophylaxis of DVT. Incidence of Heparin-induced thrombocytopenia is very rare with Fondaparinux as it does not interact with platelet function and aggregation, monitoring of prothrombin time or partial thromboplastin time is also not required [21]. Patient on fondaparinux should be watched for bleeding and thrombosis risks. [22]

Dabigatran etexilate is the prodrug of dabigatran which is rapidly absorbed from the GIT has a bioavailability of 5% to 6%. The drug has a half-life of 8 hours after single-dose and it is excreted predominantly by the kidneys. It produces a predictable anticoagulant effect, and hence it does not require coagulation monitoring. Dabigatran has been approved for VTE prevention after orthopaedic surgery in Europe and Canada [23]. The RE-COVER trial compared dabigatran etexilate with warfarin for 6 months and found that dabigatran was as effective as warfarin in preventing recurrent VTE [24,25].

Rivaroxaban is a selective factor Xa inhibitor which has rapid onset of action. It has a high bioavailability of 80%. Rivaroxaban has ahalf-life of 4 to 12 hours. It has the major advantages of once daily oral dosing and requires no laboratory monitoring [23]. Other drugs in this group are apixaban and edoxaban. Oral anticoagulation with warfarin can be commenced preoperatively, at the time of surgery, or postoperatively for the prevention of VTE. Warfarin is contraindicated in antepartum thromboprophylaxis as it crosses the placenta and will result in teratogenicity [26]. However,Warfarin is safe during lactation [27]. Heparin is safe and it is recommended both in pregnancy and lactation [28].

The use of aspirin alone is not recommended nowadays for thromboprophylaxis against VTE. The duration of thromboprophylaxis depends on the probability for the patient to develop VTE. For high risk patients prolonged thromboprophylaxis i.e., beyond 10days and upto 35 days is recommended., whereas in patients with acute medical illness thromboprophylaxis should be continued until discharge [29,30].

Modified Caprini risk assessment tool scoring system is useful to predict VTE.

- In very low risk patients - no DVT prophylaxis is needed
- low risk patients - only mechanical method is advised
- Moderate to high risk patients - pharmacological agents with or without mechanical device is advised.[31]

Evidence Based Approach For Diagnosis Of Dvt

In early stages patient remains asymptomatic. Pain, limb edema, phlegmasiaceruleadolens, phlegmasia alba dolens, Moses' sign- pain is elicited by squeezing the calf muscles, Homan's sign- pain produced on dorsiflexion of foot.

Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	- 2

In patients with symptoms in both legs, the more symptomatic leg is used.

Table 1: Well score for predicting pretest probability for deep-vein thrombosis[32]

"DVT unlikely" if the clinical score is ≤1 and "DVT likely" if the clinical score is ≥2

Workup For Dvt

D- dimer assay is the best biomarker for the initial assessment of suspected VTE. D-dimer is a degradation product that is formed immediately after thrombin-generated fibrin clots degraded by plasmin. D- dimer levels are highly sensitive but not specific in diagnosing VTE as it is elevated in other conditions like inflammation, pregnancy, malignancy and in elderly hence its effectiveness is decreased with increasing age [33]. In patients presenting with symptoms suggestive of VTE, the combination of clinical risk stratification and a D-dimer test can exclude VTE without the need for additional investigations. Even in patients with clinically suspected recurrent DVT, clinical evaluation and D-dimer has proved to be useful for excluding DVT [34]. Elevated D-dimer is associated with poor outcome.

Venous ultrasonography is noninvasive, safe, easily available and inexpensive modality of investigation. Compression ultrasound (B-mode imaging only), duplex ultrasound (B-mode imaging and Doppler waveform analysis), and colour Doppler imaging are the three types of venous ultrasonography. The important criteria to detect VTE is failure to compress the vein lumen with gentle probe pressure or there is loss of phasic pattern where flow is defined as continuous, response to valsava or augmentation (Duplex ultrasound), and complete absence of spectral or colour Doppler signals from the vein lumen. Compression B-mode ultrasonography with or without colour Duplex imaging has a sensitivity of 95% and a specificity of 96% for diagnosing symptomatic proximalDVT [35]. For DVT in the calf vein, the sensitivity of venous ultrasound is only 73% [36].

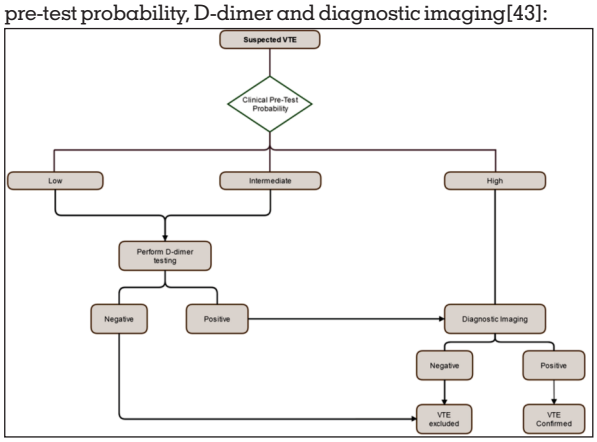
Contrast venography is the definitive diagnostic test for DVT. However it is rarely done nowadays because the non-invasive tests (D-dimer and venous ultrasound) are more appropriate and accurate to perform in acute DVT episodes. Contrast venography involves cannulation and injection of noniodinated contrast medium (eg: Omnipaque) into the pedal vein. A better deep venous filling and an improved image quality is seen when a large volume of Omnipaque is diluted with normal saline. The most reliable cardinal sign in venogram is a constant intraluminal filling defect evident in two or more views [37]. Another reliable criteria isan abrupt cutoff of a deep vein [38]. It is highly sensitive and specific in identifying the location, extent and attachment of a clot. The major disadvantages of this procedure include it being invasive and painful, exposure to irradiation, risk of allergic reaction and renal dysfunction. Occasionally a new DVT may be induced by venography, which may be due to venous wall

irritation and endothelial damage [39].

Impedance plethysmography is based on measurement of the rate of change in impedance between two electrodes on the calf when a venous occlusion cuff is deflated. Rapid change in impedance is produced when there is free outflow of venous blood, when there is delay in outflow, in the case of a DVT, leads to a more gradual change. It is a noninvasive and safe modality of investigation. It has very less sensitivity for calf thrombi and small nonobstructing proximal vein thrombi [40].

Magnetic Resonance venography (MRI) has high sensitivity in detecting calf and pelvic DVTs and upper extremity venous thromboses [41,42].In case of suspected iliac vein or inferior vena caval thrombosis the investigation of choice is MRI when computed tomography venography is contraindicated . Though there are no risk of ionizing radiation, it is costly, scarce and reader expertise is required.

Approach to venous thromboembolism (VTE) diagnosis using pre-test probability, D-dimer and diagnostic imaging[43]:



Dvt Treatment

The goal of treatment is to prevent further extension of thrombus, occurrence of acute PE, recurrence of thrombosis, development of late complications like pulmonary hypertension and post-thrombotic syndromes. Mostly Low Molecular Weight Heparin (LMWH) is preferred over Unfractionated Heparin (UFH) because of its greater bioavailability, predictability and dose-dependent plasma level, less risk of bleeding, Lower incidence of heparin-induced thrombocytopenia & heparin-induced osteoporosis can be safely administered in outpatient without laboratory monitoring, duration of anticoagulant effect is longer, permitting once- or twice-daily dosing. LMWH will be excreted by kidneys and it is not preferred in patients with renal failure. UFH is advised for renal failure patients. Warfarin remains the drug of choice for prevention of clot formation with exemption in pregnancy and in cancer patients as it is contraindicated. LMWH is preferred in pregnancy and in cancer patients[44]. In cancer patients treated with chemotherapy, the use of LMWH as primary thromboprophylaxis reduced the incidence of symptomatic VTE [45].

Before commencement of Thrombolytic therapy, the risk benefit ratio should be assessed as there is high risk for intracranial hemorrhage. Thrombolytic therapy is indicated in patient with massive DVT who are at risk for threatened limb loss. Thrombolytic agents are streptokinase, urokinase and tissue plasminogen activator.

In adjunct to medical therapy Catheter Directed Thrombolysis (CDT) can be used in the treatment of DVT [46].Tone enden et-al described additional treatment with catheter-directed thrombolysis (CDT) using alteplase reduces development of Post thrombotic syndrome in patients with a high proximal DVT and low risk of bleeding [47].There was 36-64% improvement in the patency of ileofemoral vein in patients with Catheter directed thrombolysis than those treated with anticoagulation therapy alone[48].CDT via popliteal access has been proved safe, has removed clots and restored the patency [49].Early efficacy and follow-up patency are of importance to reduce the risk for Post thrombotic syndrome.

Percutaneous endovenous intervention plus anticoagulation and low dose aspirin may be superior to anticoagulation-alone in the reduction of VTE and PTS at 6 months for patients with symptomatic proximal DVT, this has also been associated with very low risk of bleeding and promotes early discharge [50,51].

Inferior vena cava filters are recommended where anticoagulant usage is absolutely contraindicated which include intracranial hemorrhage, overt gastrointestinal bleeding, retroperitoneal hemorrhage, massive hemoptysis, cerebral metastases, massive cerebrovascular accident, and significant thrombocytopenia (<50,000/ μL)[52].Only in a small proportion of patients with VTE, retrievable filters are recommended provided anticoagulation should be initiated as soon as its placement and it is advised to remove them shortly [53].

Iliac vein stenting has become a promising new technology for treating advanced chronic venous disease. Wallstent™ has been the widely used stent and has an excellent long-term patency with good clinical outcome. However it is highly prone to compression/migration of the upper end of the stent requiring further reinterventions[54].A technical modification in which a Gianturco Z stent™ is added to the upper end of the Wallstent stack that may ameliorate some of these concerns is described.Key points in the management of venous thromboembolism (VTE) from the American Society of Hematology (ASH) 2020 guidelines [55]

The ASH guidelines suggest offering home treatment over hospitalization in patients with uncomplicated acute DVT and acute PE. This includes patients at low risk based on the Pulmonary Embolism Severity Index (PESI). Patients with sub-massive (intermediate-high risk) or massive PE as well as patients at high risk for bleeding may benefit from hospitalization.

Recommended first line of treatment for acute DVT or PE is the use of direct oral anticoagulants (DOACs). DOAC therapy is preferred over vitamin K antagonists (VKAs) for patients without severe renal insufficiency (creatinine clearance <30 ml/min), moderate-severe liver disease, or antiphospholipid antibody syndrome. The ASH guidelines suggest anticoagulation therapy alone in patients with proximal DVT. However, it is reasonable to consider Thrombolysis in patients presenting with limb-threatening DVT (phlegmasiaceruleadolens) and in selective younger patients at low bleeding risk with iliofemoral DVT. Anticoagulation therapy alone is preferred for patients with acute PE and evidence of right ventricular dysfunction (by echocardiography and/or biomarkers. Patients with extensive DVT, thrombolysis is considered appropriate, the ASH guidelines suggest using catheter-directed thrombolysis over systemic thrombolysis whereas for patients with acute PE they suggest using systemic thrombolysis over catheter-directed thrombolysis partially due to a paucity of randomized trial data.

For patients with proximal DVT and significant pre-existing cardiopulmonary disease as well as patients with PE and hemodynamic compromise, the ASH guidelines suggest anticoagulation alone over anticoagulation plus inferior vena cava (IVC) filter placement. The use of retrievable IVC filters is appropriate for patients with a contraindication to anticoagulation. The ASH guidelines define the treatment period of acute DVT/PE as "initial management" (first 5-21 days), "primary treatment" (first 3-6 months), and "secondary prevention" (beyond the first 3-6 months). The guidelines favor

shorter courses of anticoagulation (3-6 months) for acute DVT/PE associated with a transient risk factor, indefinite anticoagulation for patients with unprovoked DVT/PE or DVT/PE associated with a chronic risk factor.

The ASH guidelines does not suggest the routine use of prognostic scores like D-dimer testing, venous ultrasound to guide the duration of anticoagulation treatment. For patients with breakthrough DVT and/or PE while on therapeutic VKA treatment, the ASH guidelines suggest using low molecular weight heparin over DOAC therapy. This does not apply to patients who experience breakthrough DVT/PE due to poor international normalized ratio.

The ASH guidelines suggest suspending aspirin therapy when initiating anticoagulation in patients with DVT/PE with stable cardiovascular disease. The combination of anticoagulation plus aspirin increases the risk of bleeding without clear evidence of benefit for patients with stable cardiovascular disease.

The ASH guidelines does not recommend the routine use of compression stockings in patients with acute DVT not at risk for post-thrombotic syndrome. However, selected patients may benefit from compression stockings to help reduce edema and pain associated with acute DVT.

Complications Of Dvt

The complications of DVT include development of Pulmonary embolism (PE) ,Paradoxical emboli, Recurrent DVT, Post thrombotic syndrome. Approximately 4% individuals treated for DVT develop PE. It accounts for 10-12% mortality rate in hospitalized patients [56,57]. Clinically, PE presents as abrupt onset of pleuritic chest pain, shortness of breath and hypoxia, sometimes patient maybe asymptomatic [58]. Physical signs like tachypnea (>20 breath/min), rales, tachycardia, accentuated s2, fever, limb edema, cyanosis maybe present. ECG shows abnormalities of ST – T wave [59].

Computed Tomography Angiography is the investigation of choice for diagnosing PE. Patients with PE should receive LMWH or Fondaparinux instead of UFH. Paradoxical emboli occur in patients with atrial septal defect are at high risk for the passage of emboli to the arterial circulation and result in stroke. Almost half of patients who have not been treated for DVT develop recurrent, symptomatic venous thromboembolism (VTE) event within 3 months with pain and edema.

Recurrence proportionally increases the risk of post thrombotic syndrome (PTS). Postthrombotic syndrome (PTS) is one of the chronic complications of deep venous thrombosis (DVT) which manifests later in life. Symptoms include mild erythema, localized induration or even massive extremity swelling and ulceration. It is usually exacerbated by standing and relieved by elevation of the extremity. The incidence of PTS is 25-50% within 2 years despite long-term anticoagulation for iliofemoral DVT, and after 7-10 years, the incidence is 70-90%. [60,61]

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