Postoperative Thrombosis and Its Investigations: An Overview of Pathophysiology, Natural Coagulation Inhibitors, Risk Factors and Laboratory Investigations

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Abstracts

Background: One of the most frequent and fatal complications post-surgery is thrombosis or Deep Vein Thrombosis (DVT). It encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), which can lead to considerable morbidity and mortality if undiagnosed or untreated. Understanding the clinical features and diagnostic approach, including laboratory investigations, is critical in managing this condition effectively. DVT can lead to serious complications like pulmonary embolism, venous gangrene, and post-thrombotic syndrome to name a few. These complications affect the post-recovery journey and overall quality of life of the patient. Objective: This review aims at overviewing the Thrombosis, associated risk factors, and corresponding lab investigations. Methods: The review is comprehensive research of PUBMED and Google scholar from the year 1965 to 2024. Conclusion: Multidisciplinary collaboration among surgeons, physicians, and laboratory specialists is vital to optimize outcomes and reduce the burden of thrombotic complications in postoperative patients.

Keywords: Deep venous thrombosis, Thrombophilia, Virchow’s triad, D-dimer, Factor V Leiden, Hyperhomocysteinemia.

Introduction

One of the most frequent and fatal complications post-surgery is thrombosis or Deep Vein Thrombosis (DVT). It encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), which can lead to considerable morbidity and mortality if undiagnosed or untreated. The pathophysiology of post-operative thrombosis is multifactorial, involving immobility, hypercoagulable states, and endothelial injury. Understanding the clinical features and diagnostic approach, including laboratory investigations, is critical in managing this condition effectively. DVT can lead to serious complications like pulmonary embolism, venous gangrene, and post-thrombotic syndrome to name a few. These complications affect the post-recovery journey and overall quality of life of the patient. [1]

Around 0.2% of the overall patients and 25% of patients admitted to hospitals post-surgery are affected by DVT.[1] Thromboprophylaxis has considerably reduced the incidence of DVT, the numbers going up to 50-70% before its advent post certain surgeries. Around half the patients suffering from acute proximal DVT develop post-thrombotic syndrome (PTS) in the first 1-2 years as a complication.[2] Following a routine use of tourniquet after varicose vein surgery the incidence of DVT was shown to be around 7.7%. The most common occurrence of DVT is seen in the deep veins of the lower extremity with the most affected vein being the muscular calf vein followed by popliteal superficial and common femoral veins. [2] The risk of DVT increases around 5-10% with pregnancy. The first and second trimesters have a moderate risk followed by increased risk in the third trimester. [3] The risk of DVT increases further after operative delivery. Surgical procedures like craniocerebral surgery due to its prolonged duration of procedure pose a higher risk of DVT ranging from 5-60%. Other surgeries like orthopedic, gastrointestinal, and urological surgeries have also been shown to be risk factors for DVT. [4]. Immediate use of anticoagulation therapy after surgery has been shown to decrease the occurrence of DVT although it is debatable and is associated with a higher risk of fatal cerebral hemorrhage and also considerably increases the cost of treatment. Some studies stand against the use of anticoagulants and advocate the use of mechanical techniques alone to prevent DVT post-surgery. This review discusses in detail the risk factors, lab investigations, and prevention strategies of postoperative thrombosis. [5]

Pathophysiology of Thrombosis

Three main factors contribute to the development of thrombosis and blood clots. These three factors together form the Virchow's triad which initiates the postoperative thrombosis.

Hypercoagulability: This is the state of the body where blood is more likely to form clots. During surgery, there is an increased inflammatory and coagulation cascade leading to a pro-thrombotic state.

Endothelial Injury: The lining of the blood vessels is damaged during surgery, particularly the orthopedic and vascular surgeries thus leading to increased formation of clots.

Venous Stasis: The risk of clot formation increases after surgeries due to prolonged immobility which reduces the venous return. [6]

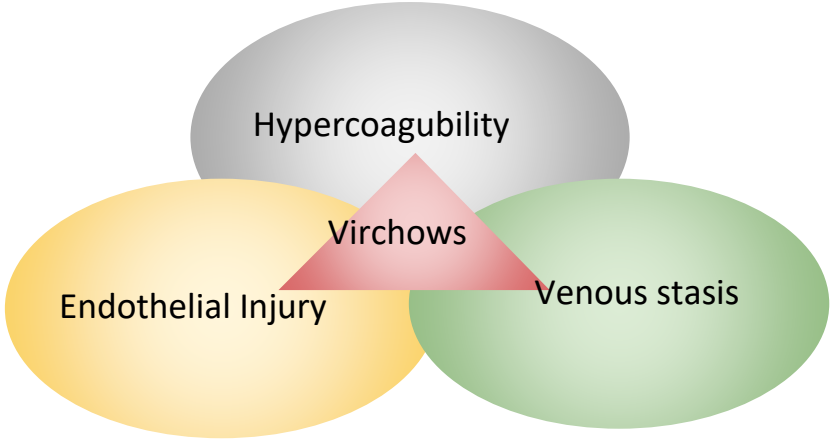

Figure 1: The chart of Virchow's Triad [6]

Clinical Presentation of DVT

Patients with postoperative thrombosis may exhibit variable clinical signs depending on the location and severity of the thrombus:

Deep Vein Thrombosis (DVT): Swelling, pain, tenderness, and erythema, commonly in the lower extremities.

Pulmonary Embolism (PE): Sudden-onset dyspnea, chest pain, tachycardia, hemoptysis, and in severe cases, hemodynamic instability.

Risk Factors associated with the occurrence of DVT

In a study conducted by Su ZJ et al [5], 8 independent risk factors for DVT post craniocerebral surgery were identified, listed below:

1. Age
2. D-dimer
3. Post-operative infection
4. Post-operative Caprini score
5. Duration of the surgery
6. Intraoperative blood transfusion
7. Post-operative cortisol application
8. Intraoperative Intermittent pneumatic compression (IPC)

American College of Chest Physician Evidence-based Clinical Practice Guidelines (ACCP) in 2008 came up with a set of risk factors [Table1] [7]

Table 1: Risk factors for venous thrombosis according to ACCP (2008) [7].

1.	Older age group
2.	Decreased mobility or paresis
3.	Previous history of VTE
4.	Ongoing cancer or chemotherapy
5.	Surgery
6.	Trauma
7.	Obesity
8.	Inflammatory bowel syndrome
9.	Central venous catheter
10.	Pregnancy or post pregnancy
11.	Oral contraceptives or estrogen therapy
12.	Acute medical illness
13.	Nephrotic Syndrome

Older age groups have a higher incidence of thrombosis. Although D-dimer has a very high false positive rate because of elevated levels in older age groups and patients with tumors and infections, it is still the most convenient and cost-effective method for detecting DVT. If a patient presents with an elevated D-dimer reading, a lower extremity venous ultrasound should always be advised to detect the presence of lower extremity DVT. [8]

Infections cause an increased release of cytokines which further triggers the release of inflammatory factors, monocytes, and platelets. These factors further increase blood coagulation and fibrin formation thereby increasing the risk of thrombosis. Patients are at risk of infection-induced thrombosis for 6 months post-surgery and should be monitored closely and be prescribed the required medication for any postoperative infection. [9] The Caprini score has been shown to have a high sensitivity for predicting DVT. Patients with scores higher than 4 have shown to have a moderate probability of DVT with a higher risk in patients with scores more than 9. [10] Another contributing factor to the occurrence of DVT is venous dilatation which occurs mainly due to the prolonged duration of the surgery which causes stasis of blood. The use of muscle relaxants and intraoperative fluid infusion also causes venous dilatation thereby contributing to the incidence of DVT. In 1970, Calhan et al [11] first used IPC in a patient where they applied the IPC to the lower extremities of the patient and the regular inflation and deflation helped in blood flow back to the heart. The use of IPC during surgery in case of longer surgeries like craniocerebral surgeries decreases the incidence of postoperative DVT. IPC reduces the venous pressure by contracting the muscles which promotes arterial blood flow and reduces stasis. Tissue fluid also gets introduced in the blood circulation as the pressure within the subcutaneous tissue rises which reduces the subcutaneous edema. When craniocerebral surgeries involving functional regions are performed, patients are woken up in the middle to move their limbs thereby decreasing the chances of postoperative DVT. [11]

Laboratory Investigations

Laboratory tests are integral to the diagnosis and management of post-operative thrombosis. Common investigations include:

D-dimer Assay

D-dimer is a fibrin-specific degradation product. D-dimer helps in the detection of cross-linked fibrin which is the result of endogenous fibrinolysis and hence detects DVT. It is a sensitive and non-specific marker for predicting DVT. D-dimer has limited clinical ability due to its poor specificity. On the other hand, D-dimer has an appealing use case in an emergency room setting. In a study conducted in 2003, Anderson stated that D-dimer showed a sensitivity of 82.6% and specificity of 70% when used alone to detect the presence of proximal DVT. [12] This inference states that D-dimer should not be used alone to detect the presence of DVT and should be used as an adjunct to other techniques. In an emergency setting when a low-risk patient reports in the middle of the night with leg symptoms a D-dimer assay is done and if reported positive the patient is given a single dose of low molecular weight heparin and is recalled in the morning for duplex scan. In case of a negative D-dimer assay, the patient is recalled in the morning for a duplex scan. It should be noted that this protocol is followed only in patients with low risk, patients with moderate and high risk are given a single dose of LMWH without a D-dimer assay and recalled in the morning for a duplex scan. Low-risk patients can also be ruled out by analyzing D-dimer levels in suspected cases of pulmonary embolism as stated by Wells and colleagues. In a study conducted by Dunn et al they concluded that with a high negative predictive value of 99.6%, a negative D-dimer assay can be used to exclude PE in an emergency setting. [13]

Thrombophilia

In 1965, Egeberg coined the term Thrombophilia to describe the occurrence of venous thrombosis in a Norwegian family that had an antithrombin deficiency. [14] It was further studied by Middendorf that thrombophilia is diagnosed based on clinical symptoms like thrombosis at a young age, recurrence episodes of thrombosis, heparin resistance, skin necrosis induced by warfarin, and thrombosis at unusual sites. Patients with thrombophilia defects have been shown to have thrombotic events during pregnancy. [15]

Factor V Leiden

The most common cause of thrombophilia is resistance to activated protein C. This occurs due to a single mutation in the factor V gene which is known as factor V Leiden. [16] The factor V defect is inherited as an autosomal dominant trait. Such individuals develop resistance to proteolytic degradation and a hypercoagulable state is seen. An incidence of 3 to 7% of factor V Leiden is seen in the Caucasian population. Around 17.6% of patients with thrombosis have tested positive for Leiden defect. Heterozygotes have a threefold greater risk of thrombosis than the general population and homozygotes show a 50 to 80 times higher risk of thrombosis when compared to the general population. [17]

Prothrombin 20210A Mutation

A recently recognized mutation of the prothrombin gene (P20210A) has been seen and patients with this gene have shown to have a higher risk of thrombosis. These patients have higher levels of prothrombin because of increased synthesis and are at a 3 times higher risk for venous

thrombosis. Around 5.5% of patients testing positive for venous thrombosis and 1.2% of the general population will test positive for this mutation. [18]

Antiphospholipid Antibody Syndrome

A heterogenous group of immunoglobulins including anticoagulants and anticardiolipin antibodies is known as Antiphospholipid antibodies. One-third of the people positive with antiphospholipid antibodies show a greater tendency towards thromboembolic events. Recurrent loss of pregnancies, venous thrombosis, gangrene, myocardial infarction, and thrombocytopenia are a few such events seen in people positive with this antibody. If these patients have a history of smoking or other risk factors like hyperlipidemia, there is a high chance of recurrent strokes. [19] Neurological manifestations are also seen like cerebral infarcts, severe headaches of vascular origin, and visual disturbances like retinal artery and vein occlusion. Antiphospholipid antibody syndrome has an incidence of 2-3%in the caucasian population and around 22-69% of patients show an increased tendency towards recurrent thrombosis. [20] Such patients should be put on a lifelong prescription of anticoagulants especially when other prothrombotic risk factors are also present. Any elective surgery in such patients should be thoroughly calculated against the associated risk and patients should be counselled. In case the surgery is unavoidable these patients should be put on the strongest prophylactic regime even with the bleeding risk. [21]

Hyperhomocysteinemia

Elevated levels of homocysteine in blood have been shown to be associated with higher occurrences of arterial and venous thrombosis. Some practitioners have suggested checking for elevated homocysteine levels in patients who are planning to go for elective surgeries and patients with stroke, myocardial infarction, and DVT. Some studies have concluded that homocysteine levels tend to double the chances of DVT. [22] Patients with elevated values should be put on vitamin therapies which will lower the occurrence of venous thrombosis. Homocysteine causes endothelial damage which results in deep vein thrombosis hence measuring homocysteine levels is a better approach rather than measuring the gene that plays a role in homocysteine metabolism known as methylenetetrahydrofolate reductase. In the general population, around 30 people have shown to have heterozygous defects but no increase in the risk of thrombosis, and patients with a homozygous defect show increased risk only if the levels of homocysteine are increased. [22]

Deficiencies of Natural Coagulation Inhibitors

The very first genetic cause of Venous thrombosis was noted to be a deficiency of antithrombin protein C and protein S less than 1% population has been shown to have such deficiency, but when these coexist with other genetic abnormalities such as laden defect, the chances of thrombotic events increase manifold. [23]

Coagulation Profile

Prothrombin Time (PT) and International Normalized Ratio (INR): Assesses extrinsic and common coagulation pathways; helpful in monitoring anticoagulant therapy. Activated Partial Thromboplastin Time (aPTT): Evaluates the intrinsic and common coagulation pathways. [23]

Fibrinogen Levels

Hypofibrinogenemia may indicate disseminated intravascular coagulation (DIC), a severe thrombotic complication. [23]

Imaging-Associated Laboratory Tests

Combination with imaging studies like Doppler ultrasonography for DVT or computed tomography pulmonary angiography (CTPA) for PE enhances diagnostic accuracy. [23]

Additional Markers of Thrombophilia

Disorders of the fibrinolytic system increase the chances of VTE. Certain coagulation factors like II, VIII, IX, and XI when seen in elevated numbers have also been shown to be associated with increased risk of thrombosis. [23,24]

Thrombosis after Anesthesia

The relationship between anesthesia and thrombosis is complex, shaped by physiological changes and procedural factors. General anesthesia can increase thrombosis risk by inducing immobility, altering blood flow dynamics, and potentially suppressing fibrinolytic activity. Certain anesthetic agents may also influence coagulation pathways, either by modulating vascular tone or impacting platelet function. The risk is further compounded by patient-specific factors, such as advanced age, obesity, or a history of thrombotic events, as well as the duration and nature of the surgical procedure. In contrast, regional anesthesia such as spinal or epidural techniques may reduce thrombosis risk by preserving lower limb motor function and facilitating earlier postoperative mobilization. Recognizing these interactions is crucial for tailoring perioperative strategies, including the use of pharmacologic prophylaxis and mechanical measures like compression devices, to effectively prevent thrombosis. [25]

Conclusion

Post-operative thrombosis remains a significant clinical challenge with potentially life-threatening consequences. A thorough understanding of risk factors, vigilant clinical monitoring, and appropriate use of laboratory investigations are essential for timely diagnosis and effective management. Multidisciplinary collaboration among surgeons, physicians, and laboratory specialists is vital to optimize outcomes and reduce the burden of thrombotic complications in postoperative patients.

Author contributions

After reading the manuscript and amending the material, all authors approved its submission and agreed to take full responsibility for the work. The first author created the first manuscript, and the corresponding author, who also makes crucial changes, served as the supervisor.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Ethical Approval

Not Applicable

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