CONFERENCE PROCEEDING

# Deep vein thrombosis in neurocritical care

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## INTRODUCTION

Deep vein thrombosis (DVT) is a common complication in critically ill neurological patients and can lead to thromboembolic episodes, which can in turn lead to morbidity and can even be fatal. Although there is paucity of data on the actual incidence of venous thromboembolism (VTE) as a cause of death in Indian patients, recent evidence suggests that DVT occurs as frequently among Asians as it does among Caucasians.[1] More importantly, it is a preventable complication, and hence there is a need for greater awareness of thromboprophylaxis among treating neurophysicians and neurosurgeons. There is also a great need for neurosurgeons to understand the role of anticoagulants when the benefits outweigh the risk. Despite our better understanding and the growing body of evidence regarding the beneficial role of thromboprophylaxis among medical and neurological Intensive Care Unit (ICU) patients, there is a general gap between knowledge and actual practice.

## INCIDENCE

Although there is a great deal of variation in the statistics with regard to the overall incidence of DVT, all of the reported figures are quite high. The rate of DVT formation associated with cranial and neurosurgical spinal procedures performed without prophylactic measures varies from 29% to 43% in earlier studies.[2] Subsequent studies have shown a decline with the average incidence being around 10%. This may be attributed to some prophylactic measures being instituted routinely by neurosurgeons.[3] Hence, patients undergoing neurosurgery are at moderate risk. The highest incidence is seen in the patients of spinal cord injury [Figure 1]. In patient of stroke, the incidence can be as high as 50%.[4]

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Silent DVT is more common than we think it is and so is silent pulmonary embolism (PE). The diagnosis of DVT in critically ill neurological patients poses specific challenges to the clinician because many patients have difficulty in communicating their symptoms, or they may lack classical examination findings seen in outpatients with DVT. Moreover, laboratory markers shown to predict DVT in symptomatic outpatients do not have predictive value in critically ill patients.[5] Patients with cryptogenic stroke or transient ischaemic attack tend to have a greater risk of silent PE. Tanislav *et al*. identified patients who had a patent foramen ovale and underwent ventilation perfusion scans. They evaluated 151 patients from the 266 patient registries. A silent PE was found in 35% patients though DVT could be identified in only 7% of the patients.[6] Perhaps the greatest contributor to the reported variation of DVT risk among patients with brain tumours is the degree of clinical attentiveness. The incidence of clinical DVT appears to be much higher in centres who look for it.

## WHY ARE NEUROSURGICAL AND NEUROLOGICAL PATIENTS AT RISK?

The risk of DVT and its consequences can be separated into various factors related to the patient or to the disease.

- Factors related to the basic health and medical condition of the patient
- Factors related to the specific underlying neurological disorder
- Surgical factors.

### Factors related to the basic health and medical condition of the patient

- Age >60 years
- Bedridden patients
- Acute stroke
- Severe spinal cord injury



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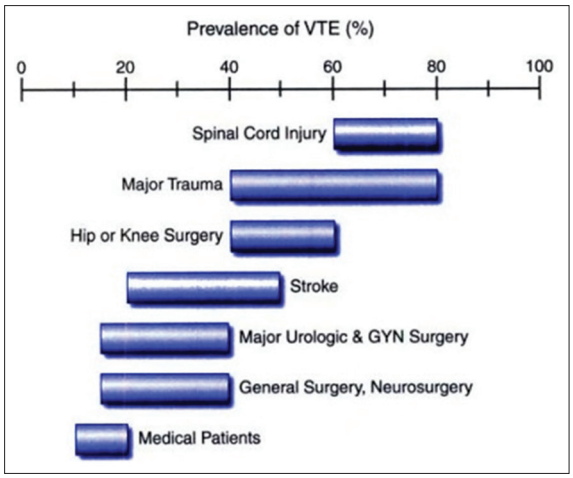


**Figure 1:** The prevalence of venous thromboembolism in a variety of patients

- Heart failure
- Previous episodes of DVT
- Obesity
- Malignancy
- History of oral contraceptive
- Deficiency of anti-thrombin III protein C or S.

### Factors related to the specific underlying neurological disorder

- Pre-operative leg weakness
- Suprasellar tumours
- Histology type of tumour
- Longer stay in the ICU both pre- and post-operative
- Delayed recovery
- Delayed initiation of mobility and activity.[7]

### Surgical factors

- Long duration of surgery
- Use of dehydrating agents
- Use of steroids
- Release of cerebral thromboplastic substances
- Central line in place for a long time
- Sepsis.

Tissues obtained in patients with intracranial tumours who experienced thromboembolic events have been shown to have an imbalance of plasminogen activator and inhibitor systems. More specifically, brain tumours have been found to inhibit plasmin, enhance release of thromboplastin and increase procoagulant and platelet aggregatory activity.[8]

In a study of 114 patients with brain tumours, Sawaya *et al*. found that total fibrinolytic activity was reduced in patients with malignant brain tumours.[9] Plasminogen and plasmin inhibitor levels did not show significant changes, but tissue plasminogen activator (tPA) was low, and plasminogen activator inhibitor-1 levels were high in a large proportion of patients. Supratentorial and suprasellar locations have increased risk with the highest incident being found in meningiomas, malignant glioma, and metastatic disease.[10]

The use of chemotherapy puts patients at high-risk than regimes that include either 1,3-bis (2-chloroethyl)-1-nitrosourea or cisplatin increase the risk of DVT and PE.[11,12]

## SCREENING METHODS FOR DEEP VEIN THROMBOSIS

### Clinical features

Clinically, calf vein thrombi are relatively benign unless they extend into the proximal veins. Isolated calf vein thrombi result in pulmonary emboli in <1% of cases, whereas thrombi in the proximal veins result in pulmonary emboli 40 to 50% of the time. Deep venous thrombosis in the lower extremities are the source of 90% of pulmonary emboli, the remainder arises mostly from DVTs in the pelvis.

The presence or absence of clinical symptoms of DVT is as unreliable marker. Swollen, tender, warm calf; venous dilation; or a positive Homan sign are associated with proven DVT in only 20–50% of patients and has a low probability of developing PE. Conversely, 50–60% of patients with DVT will not have these symptoms, a finding supported by the substantial number of those with PE, who present with no clinical evidence of DVT.[13]

### 125-labelled fibrinogen test

Radiolabelled fibrinogen is injected intravenously, where it becomes incorporated into any developing thrombus and is visible on scans. It is said to be too sensitive and detects small DVTs that resolve spontaneously.[14] In addition, it was found to be inaccurate for detection of clots originating in the pelvis and thigh, which are thought to be the most life-threatening types.

### Impedance plethysmography

A continuous uniform flow of blood produces no significant change in the electrical impedance of the body segment, whereas pulsatile blood volume changes are recorded as electrical impedance changes over time. This study is done with a pneumatic tourniquet and blood flow is studied as tourniquet is released. In the absence of calf thrombus, the electrical impedance decreases as the tourniquet is released. When there is obstruction of the proximal veins by a thrombus, on release of the tourniquet there is an increased impedance as detected on plethysmograph. Studies have shown that the risk PE in patients with negative results is 1%. The interpretation of the test is also fairly straightforward making it a useful screening tool. The only word of caution is that false-negative findings can occur in patients of non-occlusive proximal DVT and well-developed collateral vessels and hence a

second study should be repeated after 2 weeks. The advantage of impedance plethysmography over Doppler is that it is not subjected to clinical interpretation and expertise.

### Ultrasound examination of femoral veins

Doppler ultrasonography is the most common investigation available in most centres and most widely used. It detects the flow velocity of blood which can be audibly recorded. The faster the flow the higher the frequency of Doppler signals. When there is a thrombus, the flow is sluggish. In addition, a sluggish flow also shifts the spectrum of light towards blue.

When Doppler is combined with compression technique using the B-mode a cross-sectional view of the femoral artery and vein is seen. When the vein is filled with clots, the external compression fails to close the lumen. This is an abnormal sign on cross-sectional view and is an indirect evidence of venous thrombosis. The combination of Doppler and compression ultrasound is known as Duplex ultrasound. The accuracy of these methods in the diagnosis of DVT has been well-documented, especially for proximal DVT, for which a sensitivity and specificity of more than 90% has been achieved.[15] In addition, it can be used in those who have lower leg casts or amputations. The major disadvantage is that data interpretation can be highly subjective and requires a high level of skill.

### Venography

Although it is invasive, venography remains the definitive diagnostic test for DVT. Using fluoroscopy and a contrast dye, venography provides a dynamic and detailed image of the leg veins. It is extremely sensitive in identifying the location, extent and degree of attachment of a clot. Rossi *et al*. state that venography remains the only reliable diagnostic method for DVT detection in patients who are asymptomatic post-operatively.[16] However, it is not practical for routine screening. Venography exposes the patient to radiation, it is painful, and it takes approximately 30–45 min to perform. The test also carries the risk of allergic reactions and renal dysfunction and may actually produce a new DVT in approximately 1% of cases. It is recommended when Doppler results are equivocal.[17]

## STRATEGIES FOR PREVENTION OF DEEP VEIN THROMBOSIS IN NEUROCRITICAL CARE

The methods used for DVT prophylaxis are mechanical, pharmacological or a combination of both.

### Mechanical prophylaxis

Every patient should receive some form of mechanical prophylaxis. The risk of fibrinolysis and clot dislodgement is considered to be more theoretical than real. These techniques include the use of graduated compression stockings, intermittent external pneumatic calf compression, electrical stimulation of the calf muscles and rotating tables.

#### *Graduated compression stocking (TED stockings)*

They are designed to create 18 mm Hg external pressure at the ankles and 8 mm Hg external pressure at the thigh. 10 mm Hg pressure gradient acts as a driving force for venous outflow from the legs. They can be used from the start of the case in long operations. However, it should not be used as a solo measure in high-risk cases as it is the least effective method.

#### *Intermittent pneumatic compression pumps*

They are inflatable bladders wrapped around the lower leg. When inflated they create 35 mm Hg compression at the ankle and 20 mm Hg at the thigh. These devices also create a pumping action by inflating and deflating at regular intervals and further augment venous blood flow. This method is useful as a solo measure in neurosurgery patients where anticoagulants are to be avoided.

### Pharmacological prophylaxis

Heparin usage and VTE prophylaxis in general may be low due to several factors including lack of awareness among physicians of necessity of giving thromboprophylaxis, lack of institutional guidelines, lack of confidence in prescribing prophylaxis to medical-ICU and neuro-ICU patients, fear of complications such as bleeding, cost of prophylaxis and belief of low prevalence of VTE.[18,19]

The following pharmacological agents can be used.

#### *Low dose unfractionated heparin*

The standard unfractionated heparin (UFH) has molecules of varying size. Smaller molecules have more anticoagulant activity. The rationale for using this form of heparin is that small doses of heparin can inhibit thrombus formation without full anticoagulation. This is due to its anti-thrombin effect and the fact that it does not affect other coagulation factors. The other advantage is easy reversibility and safety in renal disease. The regime for low dose UFH is 5000 units subcutaneous 2 or 3 times a day. The first dose should be given 2 h before surgery and continued for 7–10 days or until the patient is fully ambulatory. The side effect is heparin-induced thrombocytopenia.

#### *Low-molecular-weight heparin*

Low-molecular-weight heparin (LMWH) is made of smaller molecules of uniform size and hence more potent and predictable anticoagulant effect than UFH. The advantages are less frequent dosing, lower risk of bleeding and heparin-induced thrombocytopenia. There

is also no need to do routine anticoagulant monitoring. It is the drug of choice in spinal cord injury.[4] Currently, there are seven LMWHs available but the two that are extensively studied for thromboprophylaxis are enoxaparin and dalteparin (fragmin) used as 40 mg subcutaneous once a day for moderate risk conditions or 30 mg twice a day for high-risk conditions and 2500 units once a day for moderate risk conditions or 5000 units once a day for high-risk conditions, respectively. The first dose is given 6 h after surgery. Pre-operative dosing was tried and abandoned due to increased bleeding.

### *Adjusted dose warfarin*

Systemic anticoagulation with warfarin is another popular method for orthopaedic surgery with an International Normalised Ratio (INR) adjustment at 2–3. It has no advantage over LMWH in neurosurgery. For patients on warfarin requiring neurosurgery, it has to be stopped 4 days before. Bridging therapy is done with LMWH. For emergency surgery, the effect of warfarin may be reversed with fresh frozen plasma, activated factor VII or prothrombin complex concentrate.

### *Fondaparinux*

Fondaparinux is a synthetic anticoagulant that selectively inhibits factor Xa. It has predictable anticoagulant effect in doses of 2.5 mg once a day subcutaneously. It does not require laboratory monitoring. The main advantage of this drug is that it does not induce immune-mediated thrombocytopenia. However, it is contraindicated in renal disease and in patients weighing <50 kg.[20]

### *Direct factor Xa inhibitors*

These are new drugs with promising results. They can be administered orally and have a rapid onset of action. Hence, they are useful in acute DVT. Clinical trials have shown a lower risk of intracranial bleeding.[21] However, the experience with these drugs is limited. Dabigatran is the only drug available for clinical use.

## RISK OF INTRACRANIAL HAEMORRHAGE WITH PHARMACOLOGICAL PROPHYLAXIS

The above-mentioned drug regimens are useful in preventing DVT and PE. However, they have to be used judiciously in each case. Many large studies have been conducted recently which provide us with diverse evidence both for and against the use of thromboprophylaxis. Following are worth mentioning in this review:

- A prospective observational study in 525 patients by Norwood *et al*. demonstrated that the risk of clinically significant haemorrhagic complications is much lower than the historical risk of DVT and PE and that traumatic brain injury (TBI) patients should be offered thromboprophylaxis[22]
- After conducting a prospective observational study of all TBI patients, the authors stressed the need for surveillance and 'alternate means for pulmonary thromboembolism prevention', rather than any prophylaxis (i.e. 'its going to happen anyway, and the real art is knowing when to shove an inferior vena cava (IVC) filter up into them')[23]
- A retrospective study of 342 patients with TBI demonstrated the safety of giving heparin if the second head computed tomography (CT) imaging looks unchanged[24]
- Saadeh *et al*. conducted a retrospective case series of 205 patients with TBI, of whom 122 had a 'stable' second CT and concluded that there was neither harm nor was there really any benefit of thromboprophylaxis.[25]
- A randomised controlled trial of low-risk TBI patients demonstrated that the use of VTE prophylaxis is quite safe[26]

## DIAGNOSIS OF THROMBOEMBOLISM AFTER SURGERY OR A NEURO-CRITICAL INCIDENT

- Chest X-ray
- Arterial blood gas
- Electrocardiogram
- Doppler examination of lower limbs for the presence of DVT
- Ventilation/perfusion scan - Useful in patients who have otherwise normal lungs
- Spiral CT angiography - High reliability and very useful in ventilated patients
- D-Dimer test - Exclusion diagnosis
- Pulmonary angiography - Most accurate but is less performed as other diagnostic modalities are available.

## TREATMENT OF DEEP VEIN THROMBOSIS AND THROMBOEMBOLISM

### Anticoagulation

Anticoagulation is the mainstay of therapy for patients with DVT. Anticoagulation is indicated for all patients with proximal DVT and select cases of distal DVT. An analysis of 1643 patients anticoagulated for acute DVT reported that the mortality rate of proximal DVT is higher than that of distal DVT (8% vs. 4%).[27] The primary objective of anticoagulation is the prevention of further thrombosis and to avoid early and late complications. Options for initial anticoagulation include the following.

UFH:

- Administered intravenously
- Bolus of 80 IU/kg followed by continuous infusion of 18 IU/kg/h

- Check PTT after 6 h
- Target a PTT of 46–70 s
- Lowered doses in patients >130 kg.

Low-molecular-weight heparin:
- Enoxaparin 1 mg/kg subcutaneous every 12 h
- Monitoring of anticoagulation is not necessary.

Warfarin anticoagulation:
- Oral warfarin on the 1st day of heparin therapy
- When INR reaches 3 the heparin can be discontinued
- Useful in cancer surgery
- May be useful in neurological conditions but not recommended for neurosurgical case.

### Thrombolytic therapy

Thrombolysis is usually reserved for life-threatening cases of PE. Thrombolytic drugs available are alteplase and reteplase. They are tPA:
- Alteplase: 0.6 mg/kg over 15 min
- Reteplase: 10 units by bolus injection and repeat in 30 min.

While there is no doubt that they are highly effective, their use in neurosurgery is very limited due to considerable risk of intracranial haemorrhage. The decision to use thrombolytic therapy following neurosurgery would be taken only when there is a life-threatening situation, and the benefit is likely to far outweigh the risk.

### Inferior vena cava filter

Mesh-like filter devices can be placed in the IVC to trap the thrombi that break loose from the leg veins and prevent them from travelling to the lungs.

It would become an option in a neurocritical care when:
- There is a contraindication to anticoagulation
- Repeated embolization in spite of anticoagulation
- The presence of a free-floating thrombus.
    - The most common is the Greenfield filter.

### Pulmonary embolectomy

Embolectomy may be a life-saving measure in haemodynamically unstable PE in whom thrombolytic therapy is contraindicated. It is also a therapeutic option in those who fail thrombolysis. Emboli can be removed surgically or with an interventional technique. The clinical scenario is expected to be complicated be it a patient of stroke or following neurosurgery. It would be prudent to ensure that the patient's family understand the high risk involved.

## CONCLUSION

'The two words best characterize mortality and morbidity due to VTE in the United States; Substantial and Unacceptable Kenneth M Moser MD'.

This statement may be very apt but the concerns when dealing with even a small amount bleeding in the brain is far more complex. A review of the latest literature with meta-analysis of several large studies still does not give the practitioner to give routine thromboprophylaxis.

To conclude from a 2014 BJS article: TEDs and anticoagulation used together halved the risk of DVT/PE and doubled the risk of bleeding.

### Established guidelines

The Brain Trauma Foundation recommended (with 2007 evidence) the combined used of chemical and mechanical VTE prophylaxis in TBI patients.

The 2015 review by Abdel-Aziz refines this recommendation further:[28]
- Chemoprophylaxis should not be given within 3 days of injury for moderate risk or high-risk ICH
- Chemoprophylaxis is reasonable when low-risk patients have not developed ICH expansion within 48 h post-injury
- Chemoprophylaxis is also acceptable after day 3, when low-risk patients develop ICH expansion within 48 h post-injury
- In diffuse axonal injury patients who have not developed ICH within 72 h, chemoprophylaxis is reasonable
- DVT proportions significantly increase when chemoprophylaxis is withheld for >7 days.

Thus, each practitioner of neuroanaesthesiology needs to understand the recommendation and use it for the best possible care of the patient.

Mechanical prophylaxis must always be used, and thromboprophylaxis must be considered and discussed with the neurosurgeon and used when indicated, safe and beneficial.

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### Conflicts of interest

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