Management of Venous Thromboembolism

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Abstract

Introduction: Venous Thromboembolism is an important healthcare problem the world over, resulting in significant morbidity, mortality and resource expenditure. The rationale for use of thromboprophylaxis is based on solid principles and scientific evidence. Indian perspective on this topic is lacking due to the non-availability of published Indian data. This document reviews the available International and Indian data and discusses the relevance of recommendations for prevention and management of Venous Thromboembolism (VTE) in the Indian context.

Materials and Methods: Meetings of various specialists from different Indian hospitals in the field of Gastrointestinal Surgery, General and Vascular Surgery, Hematology, Intensive Care, Obstetrics and Gynecology, Oncology, and Orthopedics were held in the months of August 2005 to January 2006. The guidelines published by American College of Chest Physicians (ACCP),1 the International Union of Angiology (IUA),2 and the Royal College of Obstetricians and Gynecologists (RCOG),3 were discussed during these meetings. The relevance of these guidelines and the practical implications of following these in a developing country like India were also discussed. Any published data from India was collected from data base searches and the results, along with personal experiences of the participating specialists were discussed. The experiences and impressions of the experts during these meetings have been included in this document.

Results: The suggestions formulated in this document are practical, and would intend to serve as a useful practical reference.

Conclusions: A number of unanswered questions remain in the field of thromboprophylaxis, and carefully designed research protocols may help answer some of these. Implementation of the suggestions outlined in the document remains to be studied in the Indian context. ©

INTRODUCTION TO VENOUS THROMBOEMBOLISM

Venous Thromboembolism (VTE), which consists of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), is a potentially fatal disease. Long term sequelae particularly post phlebitic syndrome (PPS) are frequent and often disabling.4

The factors that predispose to Venous Thrombosis were initially described by Virchow in 1856 and are called Virchow’s triad. These factors are venous stasis, damage to the vessel wall and hypercoagulability.7 A variety of clinical conditions are associated with increased risk of venous thrombosis (Table 1).

DVT occurs less frequently in the upper extremity than in the lower extremity. The incidence of upper DVT is increasing because of greater utilization of indwelling central venous catheters. The diagnosis of DVT of the calf is often difficult to make at the bedside. This is so because only one of the multiple veins may be involved, allowing adequate venous return through the remaining patent vessels.

The initial aim of treatment of DVT is prevention of thrombus extension and PE. The long term goal is to decrease the incidence of recurrent VTE, PPS and chronic Thromboembolic Pulmonary Hypertension.

The need for systemic thromboprophylaxis, especially in surgical patients is based on the high prevalence of postoperative DVT and PE, the frequent silent presentation of VTE and the potential for major adverse
clinical outcomes. In acutely ill medical patients, thromboprophylaxis has shown to reduce the incidence of VTE as seen in MEDENOX Study. However, the utilization of thromboprophylaxis in our country has been sub-optimal. One of the reasons for this underutilization is the perception that the incidence of VTE in the Indian subcontinent is lower than seen in the western world. This perception may be due to lack of reporting of all diagnosed cases, sub optimal follow up of our patients, and the fact that a majority of thromboembolic events are clinically silent and may be often missed unless investigated for by the clinician. Moreover, the patients may not report with the diagnosis of VTE to their treating doctors, and may be seen at other hospitals or departments.

Another reason for the underutilization is the fear (among the treating doctors) of bleeding complications associated with thromboprophylaxis. This is an unfounded fear, since, if optimally utilized, major bleeding episodes may be rarely encountered.

Meta analysis and randomized controlled trials (RCT)
have demonstrated either no increase or a small increase in the absolute rates of major bleeding with the use of Low Molecular Weight Heparin (LMWH).3

From an economic point of view, it is difficult to justify the routine use of thromboprophylaxis in clinical practice, but role of thromboprophylaxis, especially in orthopedic surgery, high risk pregnancies, acutely ill medical patients, etc. cannot be ignored. Studies have proven the cost effectiveness of this treatment3, keeping in mind the increased cost incurred during hospitalization for treatment of a symptomatic patient. The use of Low Molecular Weight Heparin to treat selected patients with VTE outside the hospital has the potential to dramatically reduce the cost of health care.10

INCIDENCE OF VENOUS THROMBOEMBOLISM IN INDIAN SCENARIO

Venous thrombosis may occur in more than 50% of patients undergoing surgical procedures, particularly those involving the hip and knee; and 10% to 40% of patients who undergo abdominal or thoracic operations.12

The annual incidence of Venous Thromboembolism is approximately 0.1%; the rate increases from 0.01% among people in early adulthood to nearly 1% among those who are at least 60 years old.13 More than half of these events involve Deep Vein Thrombosis.

Patients with ischaemic stroke have an overall 42% incidence of DVT in the paretic or paralyzed leg.14

A study done in 19 centers across Asia15 showed that rate of venographic thrombosis in the absence of thromboprophylaxis after major joint surgery in Asian patients was 41%, which is similar to that previously reported in patients in western countries. This study is further supported by another small study done on 88 patients16 that showed the prevalence of post-operative DVT similar to that in western population (50% - 75%). In another study DVT was detected in 10% of 146 Korean patients undergoing cement-less THA.17

Though the exact incidence is not known in the Indian subcontinent, the clinical relevance and incidence is not expected to be any different from the Western population.

In one retrospective study, the incidence of VTE is reported to be 28% in South Indian population.18 Another retrospective study also emphasized the significant (1.79 per thousand – general population) incidence of DVT in India.19 Contrary to this, a subsequent small prospective study20 has shown that incidence of DVT in Indian patients is very low and is not comparable with American and European populations. They further concluded that it is not cost effective to advise prophylaxis in Indian patients undergoing Total Hip Arthroplasty (THA) / Total Knee Arthroplasty (TKA) who have no known risk factors for DVT.

Another study done in 104 Indian patients21 revealed that incidence of venographically proven DVT in orthopedic population is 72.2% in patients undergoing TKA followed by those with THA (42.9%) and an overall incidence of 60% in the non-prophylaxis group. These figures are in accordance with earlier studies both in Asia, Europe and North America showing a high frequency of sub-clinical DVT after major joint surgery.

A prospective observational study on epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis (The SMART Study) done on 2420 patients reveals that the incidence of symptomatic VTE in Asian patients is not low and is consistent with the rate observed in western countries.22

A retrospective study done on 100 patients to study the utilization of DVT prophylaxis in medical / surgical intensive care units10, highlighted the fact that prophylaxis is not administered to roughly one out of two critically ill patients who are eligible for VTE prophylaxis. This was carried out in State of Art Intensive Care Units in the metropolitan city of Kolkata, in India. The utilization varied from 40%-60% in different centers. This data is in accordance with some western data that cites similar incidences of underutilization.

In a registry prospective registry on venous thromboembolic events (PROVE) conducted in 19 countries23, 3526 patients with symptomatic DVT were enrolled; out of which 667 were from India. Baseline characteristics for Indian patients were similar to those observed in the overall PROVE population. Compared with the overall PROVE population, the prevalence of previous DVT, PE, or superficial leg thrombosis was similar in Indian patients, but fewer Indian patients had varicose veins (8% vs. 22%). Most enrolled Indian patients were located in acute care hospitals when DVT symptoms occurred (54%) or at home (43%). This contrasted with the overall PROVE population in which most enrolled patients were at home (60%), followed by acute care hospitals (36%). DVT was found both proximally and in the calf in 54% of Indian patients, only proximally in 17%, and only in the calf in 13%, compared with 52%, 18%, and 24% in the overall PROVE population, respectively.

DVT was idiopathic in 43% of patients, following a precipitating event in 52%, and recurrent in 6% (44%, 49%, and 9% for the overall PROVE population, respectively). Prior VTE prophylaxis had been given to only 5% of enrolled Indian patients (12% in the overall PROVE population).24

Patients with symptomatic DVT in India in the PROVE registry had similar baseline characteristics and medical histories to patients enrolled in other countries. However, very few enrolled patients (5%)
had received prophylaxis prior to their DVT event, perhaps representing poor awareness of the risks for VTE in these patients. These findings, together with continued uncertainty about the natural history of post-operative DVT in Asian populations, re-emphasize the need for randomized and preferably placebo-controlled evaluations with clinical outcome measures to establish if thromboprophylaxis is required after major joint surgery and other ‘high risk’ indications in Asia, as it is in the west.

Radionuclide Venography with Pulmonary Scintigraphy is a single modality, which can assess the entire venous tree from the popliteal, femoral, iliac vein, IVC & pulmonary arteries. Concept of total thrombus load based on above investigations may help clinician decide regarding further invasive interventional therapeutic options.24

**DVT Free Hospital Project:** With an aim to ensure timely recognition of VTE, and awareness amongst the medical community, a DVT Free hospital project is being started in Sir Ganga Ram Hospital, which is one of the tertiary care multi-speciality hospitals in India. All patients admitted for surgery in any of the participating specialty departments would be subjected to a risk assessment on the basis of a questionnaire and examination findings. All patients in the high-risk group would undergo pre and postoperative Real time B Mode Compression Ultrasonography screening to exclude DVT. All high-risk cases would be followed up for three years (Personal Communication, Parakh R. 2006).

**Normal Hemostasis**

Accurate diagnosis and treatment of patients, either bleeding or thrombosed, require the knowledge of the pathophysiology of hemostasis. The process can be divided into primary and secondary components and is initiated when trauma, surgery or disease disrupts the vascular endothelial lining and blood is exposed to sub endothelial connective tissue.

Primary hemostasis involves platelet plug formation at the site of injury. The vessel wall injury exposes tissue factor on the surface of the damaged endothelium. The tissue factor interacts with plasma factor VII, thus activating the coagulation cascade, which produces thrombin by stepwise activation of a series of proenzymes as shown in Fig. 1. Thrombin converts soluble fibrinogen to fibrin; activates factors V, VIII, and XI, which generates more thrombin; and stimulates platelets. Thrombin, by activating factor XIII, also forms cross-linked bonds among the fibrin molecules, which stabilizes the clot. Regulation of the cascade at the site of injury is thought to be due to natural anticoagulants, such as tissue factor pathway inhibitor, the protein C and protein S system, and antithrombin.25

A high Wells Score26 substantially increases the likelihood of DVT and indicates that definitive diagnostic testing is appropriate. A low Wells Score26 substantially decreases the likelihood of DVT and indicates that a simple noninvasive test, such as the D-dimer assay, may be sufficient to rule out DVT.27

Secondary hemostasis consists of the reactions of the plasma coagulation system that results in fibrin formation. As the primary hemostasis plug is being formed, plasma coagulation proteins are activated to initiate secondary hemostasis.

The sequence of coagulation protein reactions that culminate in the formation of fibrin is described as ‘Cascade’. The coagulation cascade is a highly coordinated and regulated series of linked enzymatic reactions that involves the sequential activation of plasma zymogens to resume proteases.

Two pathways of blood coagulation have been recognized; the extrinsic or tissue factor pathway and intrinsic or contact activation pathway. These two pathways of activation of the coagulation cascade converge to form a ‘common’ pathway, which leads to the generation of the pivotal coagulation enzyme.
Thrombin. Thrombin not only catalyzes the conversion of fibrinogen to fibrin but also plays an important role in sustaining the cascade by feedback activation of coagulation factors at several strategic sites.

**THROMBOPHILIA**

Thrombophilia is a term used to describe a group of conditions in which there is an increased tendency, often repeated over an extended period of time, for excessive clotting.

Thrombophilia are of two types: Inherited & Acquired.

**Inherited Thrombophilia**

Inherited Thrombophilia (Table 2) refers to a genetic problem that causes the blood to clot more easily than it should. Different factors in the blood clotting process may be involved, depending on the exact type of genetic problem present. Some types of inherited thrombophilia, such as deficiencies of antithrombin, protein S or protein C, usually are associated with venous thrombosis in people less than 50 years of age, while others, such as factor V Leiden or the prothrombin gene mutation, can predispose to a first thrombosis in all age groups.

- Factor V Leiden: It is the most common inherited thrombophilia with its prevalence as high as 20% to 40% in patients with VTE. It results from a single mutation in factor V gene. Interestingly it appears to be a stronger risk factor for DVT than PE.
- Prothrombin Gene Mutation: Like Factor V, PTG 2021OA is associated with an increased risk of VTE.
- Antithrombin Deficiency: Inherited Antithrombin Deficiency can be due to a quantitative (type 1) or a qualitative (type 2) abnormalities. It as a predominantly a risk of VTE. Approximately 60% of patients with antithrombin deficiency will have an episode of venous thrombosis by age 60 years.
- Protein C and S Deficiencies: Deficiency of these factors, are a risk for VTE and are usually associated with Factor V Leiden thrombophilia.
- Homocysteine: In assessing VTE risk, 2 metaanalysis found a 2.5 to 3 pooled odd ratio of VTE in individuals with an elevated fasting homocysteine levels.

**Acquired Thrombophilia**

There are a number of other conditions that can cause a person to be at increased risk to develop a venous thrombosis. These conditions include:

- Previous surgery (especially orthopedic surgery and neurosurgery).
- Trauma.
- Pregnancy.
- Obesity.
- Use of certain medications, including birth control pills, hormone replacement therapy etc. Third generation oral contraceptives which contain less estrogen and a different progestin are associated with a two fold increased risk of VTE compared to second generation products.
- Immobilization.
- Cancer.
- Heart failure.
- Certain disorders of the blood, such as polycythemia vera or essential thrombocytethemia.
- Kidney problems, such as nephrotic syndrome.
- Antiphospholipid antibodies (antibodies to certain phospholipids binding proteins like ACA, LAC etc. in the blood that can affect the clotting process).
- A previous episode of thromboembolism, such as a clot in the leg (deep vein thrombosis) or lung (pulmonary embolism).

**Thrombophilia Investigation and Its Timing**

A thrombophilia screen may be done on patients at admission. Follow-up testing may be needed for patients with functional deficiency on APT, APTT; or in case of abnormal protein C, protein S, APCR & AT-III.

The same screen may be repeated, or, advised for, at the end of the period of anti-coagulant therapy, or 4 weeks after withdrawing oral anticoagulant therapy. At this time, patient may or may not be on

<table>
<thead>
<tr>
<th>Genetic Conditions in Inherited Thrombophilia</th>
<th>Prevalence in patients with VTE (%)</th>
<th>Testing Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden Mutation (most common)</td>
<td>20-40</td>
<td>Screening: Activated protein C resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confirmation: Genetic testing</td>
</tr>
<tr>
<td>Prothrombin gene mutation (2021OA)</td>
<td>6</td>
<td>Genetic testing only</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>3</td>
<td>Screening: Protein S profile: (activity, total/free antigen)</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>3</td>
<td>Screening: Protein C profile (activity and antigen)</td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>1</td>
<td>Screening: Antithrombin profile (activity and antigen)</td>
</tr>
<tr>
<td>Methylene Tetra Hydro Folate Reductase (MTHFR)</td>
<td>—</td>
<td>Screening: Homocysteine level</td>
</tr>
<tr>
<td>Gene Mutation</td>
<td></td>
<td>Confirmation: MTHFR genetic testing</td>
</tr>
</tbody>
</table>
bridging heparin therapy.

- In cases with abnormal levels reported, acquired causes would need to be ruled out. Family screen may be needed for those without any acquired cause.

Physiological Anticoagulant Mechanisms

Several physiological anti-thrombotic mechanisms act in concert to prevent clotting under normal circumstances. These physiological mechanisms operate to preserve blood fluidity in the intact circulation and also to limit blood clotting to specific focal sites of vascular injury.

Endothelial prostaglandins, nitric oxides, ADPase and carbon monoxides are physiological platelet inhibitory mediators. Other anti-coagulant systems which act at different sites in the coagulation cascade to dampen fibrin accumulation are antithrombin, the protein C / protein S/ thrombomodulin systems and tissue factor pathway inhibitor (TFPI) system. Fibrin that forms despite these anticoagulant systems is then degraded by the fibrinolytic system.

Situations faced in India and present practice

- Availability and cost of these tests is a limiting factor in developing countries.
- Risk stratification and incidence of thrombosis and thrombophilia needs to be established by collecting data prospectively from multiple regional centers.

**Diagnostic Tests**

A detailed clinical examination and probability estimation, either structured (e.g. Wells’ score), or unstructured, provides useful information about the probability of DVT. In cases with a low Wells score, d dimer alone may be used to rule out DVT, whereas high Wells score may justify other invasive tests. The sensitivity and specificity of various diagnostic tests is indicated in Table 3.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast Venography</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Real Time B-Mode Compression Ultrasound</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>62</td>
<td>97</td>
</tr>
<tr>
<td>Doppler Ultrasoundography</td>
<td>59</td>
<td>98</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>59</td>
<td>98</td>
</tr>
<tr>
<td>Duplex Ultrasoundography</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td>43</td>
<td>97</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Dimer [Enzymes linked immunosorbent assay (ELISA)]</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

Diagnostic Tests for DVT include:

1. Non-invasive diagnostic tests
2. Invasive diagnostic tests

1. Non-Invasive Diagnostic Tests

Ultrasoundography imaging has both high sensitivity and specificity for the detection of thrombus in the proximal leg veins. It can be subdivided in to three categories:

i) Compression ultrasound screen: It is a definitive test as pressure applied by the scanning probe over the region of interest will compress a normal vein but not the one containing thrombus.

ii) Real time B mode compression: In this technique, normal veins appear dark, whereas a blood clot is more echogenic. In addition, the veins are typically dilated if DVT is present.

iii) Color Doppler imaging: It provides more information on both the speed and direction of flow. If there is an occlusive blood clot, it will show no flow within the vein segment or, if partially occlusive, there may be limited flow surrounding the blood clot.

Venous Ultrasonography

- Color Doppler Duplex Scan of the common femoral and popliteal vein is the most commonly used test to evaluate patients with suspected DVT. It is used in most of Indian studies. It is highly sensitive (95%) and specific (96%) for symptomatic proximal vein thrombosis. A non-compressible segment of the vein will accurately diagnose DVT.
- The main advantages are its low cost, ease of being repeated, portability of the machine, and that it can be carried out as a bedside procedure. This study done for screening of DVT in post-operative orthopedic patients when Doppler sonography and contrast venography were compared showed sensitivity of 91.66% and 100% respectively.
- Current recommendations favor the use of Duplex scanning of the entire leg. Scanning of only the proximal veins is no longer acceptable. Scanning of proximal veins alone is acceptable only if the clinical probability of thrombosis is low.

Limitations of Duplex Ultrasonography

- Accuracy depends on the observer.
- Cannot distinguish between old clot & new clot.
- Difficult to diagnose DVT in presence of significant edema or obesity.
- Less accurate in detecting DVT in pelvis or in small vessels of the calf.

Ventilation/ Perfusion (V/Q) Scan

A nuclear medicine study or V/Q scan is the primary screening tool for patients with suspected PE. The most important investigation documenting the utility...
of V/Q screening is the PIOPED study. In this study, 98% of patients with PE had an abnormality on the V/Q scan.

CT or MR angiography is rapidly supplanting V/Q scanning as 52% of V/Q scanning is indeterminate.

Problems with V/Q Scanning
- Bronchospasm in absence of PE that leads to mismatching of V/Q.
- Another cause of V/Q mismatch is chronic or unresolved PE.
- A large central or saddle embolus may also cause negative V/Q scans.

A repeat study, three months after the initial episode to be used as the patient’s new baseline is recommended.

Combination of lung scans with Radionuclide Venography for estimation of total thrombus load is a unique and reliable basis for clinicians involved in management of VTE.

Helical Computerized Tomography (CT)

CT Scan is gaining acceptance as a computer based technique for evaluation of PE. Some studies have shown that it is more sensitive than V/Q scan, 87% and 65% respectively.

Advantages of Helical CT
- The main advantage of helical CT over other methods is that it is very accurate for diagnosing other pulmonary diseases.
- Detects large PE’s, with high specificity for identification of main and lobar emboli.

Disadvantages of Helical CT
- Unable to detect smaller PE’s.
- Identification of suspicious appearing abnormalities that require further evaluation or even biopsy but actually are benign.
- Availability and cost limits its widespread use.

D-dimer

This is a non-invasive blood test to measure fibrin degradation products. The test is done using different methodologies at different institutions like ELISA techniques and new rapid methods. The ELISA method is highly sensitive (99%) for VTE when using a cut off value of 500 microgram/l. A lower value essentially excludes VTE.

D-dimer is recommended to exclude VTE in clinically suspicious patients (only for its negative predictive value). The D-dimer is useful as an adjunct to other diagnostic testing but is generally not a sufficient test to diagnose PE by itself.

Positive D-dimer assay does not raise the likelihood of DVT appreciably and therefore has limited clinical value.

Table 4: Wells’ criteria

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Immobilization for more than 3 days or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the venous system</td>
<td>1</td>
</tr>
<tr>
<td>Thigh and calf swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema (greater in the symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely or greater than that of deep vein thrombosis</td>
<td>-2</td>
</tr>
</tbody>
</table>

A score of zero or less indicates a low clinical probability; A score of one point or more indicates a moderate-to-high clinical probability

During the meetings the need was felt regarding the usage of Well’s score (Table 4) for suspected PE and use of D-dimer values, compression ultrasonography, clinical diagnosis and risk stratification for proper management of VTE.

Echocardiography

When patients with known PE undergo echocardiography, 40% will have abnormalities associated with the right ventricle. It is not a specific investigation but is a valuable bed-side test for critically ill patients with hypotension to help exclude other diagnosis such as myocardial infarction, vascular disorders, etc.

New Modalities
- Combining CT pulmonary venography with CT venography may become a very useful test in future.
- MRA – Magnetic resonance angiography has the advantage of screening for DVT and PE in one test. However it is an expensive test.
- Chest X-ray, ECG and arterial blood gases - They are non-specific but important tests for evaluating patients suspected of having PE.
- MRI – Magnetic resonance imaging is useful in detecting DVT. It is useful in patients with suspected thrombosis of the superior and inferior vena cava or pelvic veins.

2. Invasive Diagnostic Tests

Venography

- Contrast venography remains the gold standard for diagnosis of DVT.
- Findings consistent with DVT include an intraluminal filling defect in two views, or an abrupt cutoff in the contrast column in a patient with previous DVT.
- It is recommended that patients with an abnormal
ultrasound and low clinical probability of DVT or alternatively, those with a normal ultrasound in association with a high clinical probability for VTE, should be evaluated further by venography. This is cost effective as well as diagnostically confirmative.

- Radionuclide ascending venography with perfusion lung scan is very useful in assessing the total thrombus load in patients with VTE. This is the chosen investigative modality as it is a single procedure that can uniformly assess the thrombus load in the iliac, caval and pulmonary circulation, which a duplex scan with its operator dependency cannot achieve.24

- Contrast can be potentially thrombogenic, nephrotoxic or can give rise to allergic manifestations. Venography is not recommended as a screening method but to be used in evaluating patients with high clinical suspicion of DVT and a negative ultrasound, or in those patients with a non-diagnostic ultrasound who have had a previous DVT.

**Pulmonary Angiography**

Pulmonary angiography remains the gold standard for diagnosis of PE. However, the test is invasive and costly and has its side-effects.

- Gold standard but increasingly less frequently performed due to the widespread availability of CT.
- Complication rate is 1.6% (0.3 mortality- mainly in critically ill patients).
- False positive have been reported in: malignancy, sarcoid, Takayasu’s arteries and angiosarcoma.

**Drugs Affecting Coagulation**

**Classification**

1. **Anticoagulants drugs**
   - Parenteral: Low Molecular Weight Heparin (LMWH), Unfractionated Heparin (UFH).
   - Oral: Warfarin etc.
2. **Antithrombotic drugs**: Acetyl Salicylic Acid (Aspirin), Dipyridamole, Ticlopidine etc.
3. **Thrombolytic drugs**: Streptokinase, Urokinase etc.
4. **Newer anticoagulant drugs**: Fondaparinux, Idraparinux etc.

**Un-fractionated Heparin**

Standard Un-fractionated heparin (UFH) is highly sulfated glycosaminoglycan that is partially purified from porcine intestinal mucosa. Its molecular weight ranges from 3000 to 40,000 and averages 15,000.

UFH acts primarily by binding to antithrombin III, an enzyme that inhibits the coagulation factor thrombin (factor IIa), Xa, IXa, Xla and XIIa. UFH however does not directly dissolve the thrombi that already exist.

The efficacy of UFH is limited because clot bound thrombin is protected from heparin-antithrombin III inhibition. Its resistance can occur because UFH binds to plasma proteins.

An aPTT that is at least one and one half times greater than the control value should provide a minimum therapeutic level of unfractionated heparin.

The UFH requires monitoring due to its unpredictable pharmacokinetics and narrow therapeutic range. This is performed conventionally with the activated partial thromboplastin time (aPTT). However, the dose generally used to prevent VTE in high risk patients does not prolong the aPTT and therefore obviates the need for monitoring.

**Low Molecular Weight Heparin (LMWH)**

These are manufactured from standard unfractionated heparin by chemical or enzymatic depolymerization that yields fragments about one-third the size of unfractionated heparin. LMWH is selective inactivator of factor-Xa and IIa. The longer plasma half life and more predictable anti-coagulant response of LMWH preparations allow their administration as fixed dose, once daily or twice daily subcutaneous injections without need for laboratory monitoring.

**Benefits of LMWH**

The introduction of LMWH has been revolutionary for the initial treatment of VTE. When compared with Heparin, LMWH exhibits greater bioavailability after subcutaneous injection, has a longer half-life and produces more predictable anticoagulation. LMWH can be safely given subcutaneously once or twice daily, without coagulation monitoring. Meta-analysis of trials comparing subcutaneous intravenous heparin for initial treatment of VTE has shown that LMWH is as effective as heparin.33 Two more meta-analysis and randomized trials have confirmed that LMWH is at least as effective and safe as UFH for treatment of VTE.34

Besides being convenient to use, LMWH is ideally suited for OPD treatment of VTE, an approach which reduces health care costs and improves patient satisfaction and compliance.35

After more than three months of initial anticoagulant therapy, case fatality rates for recurrent VTE is about 10% after PE and 5% after DVT. The case fatality rate with major bleeding during long term anticoagulant therapy for VTE is about 10%.

Various LMWH products differ in their methods of preparation, mean molecular weight and their anticoagulant effects. This was seen by measuring the ratio of anti factor Xa to anti factor IIa (thrombin activity). The anti Xa assay is commonly used for monitoring LMWH but its clinical relevance is in doubt.36
In the absence of trials which would compare different LMWH preparations, it is unclear whether these differences are clinically important.37

**Comparability of Various Preparations of LMWH**

Although LMWH have similar mechanisms of action, their molecular weight distributions vary (Table 5) causing differences in their inhibitory activities against factor Xa and thrombin, their plasma protein binding and their plasma half lives.38,39

All these studies suggest that LMWH with similar weight profiles and hence similar specific activities are equally effective for prophylaxis as well as for treatment of DVT. The Tables 5 and 6 show the approved regulatory indications and dosages for the different LMWH available in India. The readers are referred to the product inserts for further details of each compound.

**Table 5 : Current established LMWH regimens for thromboprophylaxis**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Dalteparin (Fragmin®)</th>
<th>Enoxaparin (Clexane®)</th>
<th>Nadroparin (Fraxiparine®)</th>
<th>Parnaparin (Fluxum®)</th>
<th>Fondaparinux (Arixtra®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgery (Mod. Risk)</td>
<td>2500 IU s.c., 1-2 hrs pre-op and once daily post-op for 5-7 days or longer</td>
<td>2000-4000 IU s.c., 1-2 hrs pre-op and once daily post-op for 7-10 days</td>
<td>2850 IU (0.3 ml) s.c., 2 hrs pre-op and once daily post-op for 7 days or till ambulation</td>
<td>3200 IU s.c. 2 hrs pre-op, and 3200 IU once daily post-op for 7 days</td>
<td>2.5mg s.c., once daily not before 6 hrs post op for 7-2 days or until the patient is ambulant</td>
</tr>
<tr>
<td>General Surgery (High Risk)</td>
<td>5000 IU s.c., 8-12 hrs pre-op and once daily post-op for 5-7 days or longer</td>
<td>4000 IU s.c., 12 hrs pre-op and once daily post-op for 7-10 days</td>
<td>2850 IU (0.3 ml) s.c., 2-4 hrs pre-op and once daily post-op for 7 days or till ambulation</td>
<td>4250 IU s.c., 12 hrs pre &amp; post-op and then 4250 IU once daily for 7 days</td>
<td>2.5mg s.c., once daily not before 6 hrs post op for 7-2 days or until the patient is ambulant</td>
</tr>
<tr>
<td>Orthopedic Surgery (High Risk)</td>
<td>5000 IU s.c., 8-12 hrs pre-op, at 12-24 hrs post-op then OD for 5-10 days or 2500 IU 4-8 hours after surgery on day 1 and 5000 IU s.c. once daily from day 2</td>
<td>4000 IU s.c., 12 hrs pre-op and once daily post-op for 3 weeks</td>
<td>38 IU/kg (0.2 to 0.4 ml) 12 hrs pre and post op, then OD till D3 and 57 IU/kg (0.3-0.6 ml) from D4, OD for maximum of 10 days</td>
<td>4250 IU s.c.12 hrs pre &amp; post-op and then 4250 IU once daily for at least 10 days</td>
<td>2.5mg s.c., once daily not before 6 hrs post op for 7-2 days or until the patient is ambulant</td>
</tr>
<tr>
<td>Medical Patients (High Risk)</td>
<td>5000 IU of dalteparin s.c. once daily, for 12 to 14 days or longer in patients with continued restricted mobility</td>
<td>4000 IU s.c. and once daily for 6-14 days max, or till ambulation</td>
<td>—</td>
<td>—</td>
<td>2.5mg s.c., once daily for 6 – 14 days</td>
</tr>
<tr>
<td>Other Indications</td>
<td>During Hemodialysis and Hemofiltration Unstable Angina and non-Q wave myocardial infarction</td>
<td>During Hemodialysis Unstable Angina and non-Q wave myocardial infarction</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Where no regimen is shown the corresponding indication has not been specifically tested with the corresponding LMWH. Usually the regimen stated under General surgery is then used

Refer to the manufacturers’ guidelines for details of administration and approved dosages in each indication.

**Table 6 : Current established LMWH regimens for treatment of DVT**

<table>
<thead>
<tr>
<th>Dalteparin (Fragmin®)</th>
<th>Enoxaparin (Clexane®)</th>
<th>Nadroparin (Fraxiparine®)</th>
<th>Parnaparin (Fluxum®)</th>
<th>Fondaparinux (Arixtra®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 IU s.c. twice or 200 IU/kg s.c once a day</td>
<td>100 IU/kg s.c., twice daily or 150 IU/kg s.c once daily for a maximum of 10 days, until therapeutic anticoagulation (INR 2-3) has been achieved with oral anticoagulation therapy</td>
<td>85 IU/kg (0.1 ml/10kg) s.c., twice daily for a usual duration of 10 days, until therapeutic anticoagulation has been achieved with oral anticoagulant therapy</td>
<td>6,400 IU s.c. twice daily for at least 7-10 days. After acute phase 4250-6400 IU/day s.c. for further 10-20 days</td>
<td>Body weight adjusted dosage s.c. once daily for at least 5 days and until adequate oral anticoagulation is achieved.[5 mg for body wt &lt; 50 kg, 7.5 mg for body wt 50 to 100 kg, 10mg for body wt &gt; 100 kg]</td>
</tr>
<tr>
<td>Simultaneous anticoagulation with oral vitamin-K antagonists can be started immediately. Continue combined treatment until the prothrombin complex tests have reached therapeutic levels (usually at least 5 days).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Refer to the manufacturers’ guidelines for details of administration and approved dosages in each indication.
All LMWHs are different molecules and hence available evidence with each LMWH in a particular indication, approved regulatory status may be considered before usage in a particular condition. The US FDA also considers each of these molecules to be independent and separate drugs and not as one general group of drugs. Date of one LMWH should not be extrapolated to all others in absence of any such evidence. The tables show all the LMWHs in question along with their approved regulatory indications in India.

Cost Effectiveness

In North America, LMWH is 10-20 times more expensive than UFH. Accordingly from an economic point of view, it is difficult to justify its routine use in practice but it has been seen that LMWH is more effective in orthopedic surgery. It has also been seen that LMWH does not cross placenta and descriptive studies suggest that they are both safe and effective in pregnancy. Despite its high cost, LMWH is generally preferred over UFH because LMWH is associated with lower incidence of HIT and probably osteoporosis during long term use. The above results justify the routine use of LMWH whenever indicated. Outcome research studies have shown that although acquisition cost of LMWH is higher than that of UFH, in terms of overall cost, LMWH is more cost effective.

The use of LMWH to treat selected patients with VTE outside the hospital has the potential to dramatically reduce the cost of health care. There is need for further study in this regard to see the cost effectiveness of the use of LMWH.

Fewer patients require treatment for postoperative VT, thereby explaining why the analysis of cost effectiveness favors LMWH over UFH or Warfarin.

Complications Of Heparin

Bleeding

The major complication of Heparin is bleeding and this limits its extensive use especially in this part of the world. Factors that predispose to increased bleeding risk include advanced age, serious concurrent illness, heavy consumption of alcohol, concomitant use of aspirin and renal failure.

Due to relatively short half life of unfractionated heparin, simple discontinuation is usually adequate to control bleeding complications.

Protamine-sulphate can be used in emergency situations with serious bleeding. It is also effective in neutralizing the antithrombin activity of LMWH but does not completely reverse its anti Factor-X activity.

Heparin Induced Thrombocytopenia (HIT)

Two distinct types of thrombocytopenia are associated with heparin therapy, which are the non-immune variety and the immune variety of thrombocytopenia. The dose dependent, non immune mediated type of thrombocytopenia rarely causes severe reduction in the platelet count or clinical complications and usually does not require discontinuation of Heparin.

The immune form of HIT can cause serious limb and life threatening arterial as well as venous thrombosis. In HIT, there may be absolute or relative thrombocytopenia and it begins usually at least 4 days after initiation of therapy. It may be usually 50,000 to 60,000/cu mm. However, HIT can cause severe thrombocytopenia even in the absence of thrombosis, Heparin induced thrombosis can actually occur with a normal platelet count. Immune mediated HIT can develop with low dose heparin also.

Diagnosis of HIT

HIT remains a clinical diagnosis supported by laboratory testing. The laboratory testing involves functional assay and enzyme immunoassay of antibody to heparin-platelet-factor-4 complexes.

Management of HIT

i) Discontinue and avoid all heparin.
ii) Give a nonheparin alternative anticoagulant such as pentasaccharide (Fondaparinux).
iii) Test for HIT antibodies.
iv) Investigate for lower-limb deep-vein thrombosis.
v) Avoid prophylactic platelet transfusions.

Other Side Effects of Heparin

These are dose dependent osteoporosis, skin necrosis, alopecia, hypersensitivity reactions and hyperaldosteronism.

Advantages of LMWH over UFH

- Dose-independent clearance.
- Predictable anticoagulant response.
- No need for therapeutic monitoring apart from platelet counts.
- Less potential for adverse effects (decreased bleeding potential, less thrombocytopenia, less osteopenia).

Warfarin

It is the most frequently used oral anticoagulant. This is a derivative of coumarin and exerts its anti-coagulant action as vitamin K antagonist.

Monitoring of Warfarin

The optimal therapeutic range of warfarin for the prevention of VTE and symptomatic embolism from atrial fibrillation and tissue heart valves targets an INR of 2.0 - 3.0. Higher intensity anti-coagulation (INR 2.5 - 3.5) is required in patients with mechanical prosthetic heart valves. Although warfarin has a rapid action, its
optimal anti-thrombotic effect requires several days. So, the initial therapy is started with Heparin and then switched over to warfarin.

**Complications**

Skin necrosis may occur within the first few days but it is very rare. As with Heparin, bleeding complications are the most common adverse effects. It is related to the intensity and duration of the anti-coagulant therapy. Major bleeding on warfarin occurs at a rate of 5 to 7% per year.44

**NEWER ANTICOAGULANTS**

**Fondaparinux**

It is a chemically synthesized methoxy derivative of naturally occurring anti-thrombin binding pentasaccharide. It acts by a catalytic effect facilitating anti-thrombin binding to activated factor X. It is administered by subcutaneous injection, and its elimination half life of 17 to 21 hours allows a once daily dose. It does not bind platelets or platelet factor 4, so there is no associated HIT. There is no known antidote for reversing anticoagulant effects of Fondaparinux.

**Idraparinux**

This is a second generation pentasaccharide. It is more negatively charged than Fondaparinux. It has a very long half life so it is administered subcutaneously on a once weekly basis. It has excellent bioavailability so routine coagulation monitoring is not required.46

**MECHANICAL METHODS OF PROPHYLAXIS**

Mechanical methods of antithrombotic prophylaxis are aimed at an increasing mean blood flow velocity in leg veins and reduce venous stasis. They include:

1. Graduated elastic compression stockings (GECS).
2. Intermittent pneumatic compression (IPC) devices.
3. Mechanical foot pumps and Foot impulse technology.

There are few trials of mechanical methods in medical patients. Unlike pharmacological methods, mechanical methods do not increase the risk of bleeding and may be preferred in patients in whom bleeding risks may outweigh the antithrombotic efficacy of pharmacological prophylaxis. Mechanical methods are contraindicated in patients at risk of ischemic skin necrosis, e.g. those with critical limb ischemic or severe peripheral neuropathy.47,48 Cross-infection is a risk when devices are re-used.

**1. Graduated Elastic Compression Stockings (GECS)**

GECS are commercially available as both below-knee and above-knee stockings. Most controlled trials have used above-knee stockings.8,50,51,52 Studies comparing above-knee and below-knee stockings have been too small to determine whether or not they are equally effective.53,54,55 Hence current evidence supports the preferential use of above-knee stockings unless contraindicated (e.g. thigh circumference >81 cm, incontinence).

How to apply a compression stocking:

- The stocking should be put on early in the morning preferably before the start of the swelling.
- The leg must be dry.
- Sitting or lying down are the best positions to adopt when putting on compression stockings.
- The use of rubber gloves helps protect against tears and makes it easier to pull on.

**Contraindications and cautions for use of GECS**

Contraindications: Massive leg edema, pulmonary edema, severe peripheral arterial disease, severe peripheral neuropathy, major leg deformity, dermatitis etc.

Cautions: Correct sizes, aligning toe hole under the toe, avoid folding, not to be worn in bed.

The efficacy of GEC in prevention of post operative DVT was studied in randomized, prospective controlled trial of 200 patients, aged 40 years and above, undergoing abdominal surgery. It was concluded that GEC provided a safe and effective method of prophylaxis against DVT.57

**2. Intermittent Pneumatic Compression (IPC) devices**

IPC devices periodically compress the calf and/or thigh muscles of the leg (inflation pressures 35-40 mmHg at about 10s/min)8,50 and stimulate fibrinolysis.58 Compression devices are usually applied immediately before or during surgery and are often replaced by GECS following surgery as they can cause discomfort in the conscious patient.

Caution: Not to be used in the presence of DVT.

**3. Mechanical Foot Pumps and Foot Impulse Technology (FIT)**

The A-V impulse system foot pump has been developed to provide mechanical prophylaxis in patients who are unable to weight bear and has only been used in orthopedic surgery.

RCT data suggest efficacy in prevention of asymptomatic DVT.59–68 There is no evidence that these devices reduce symptomatic DVT or PE. Skin necrosis has been reported and discomfort from the device can lead to poor compliance.57 Compliance issues associated with the use of mechanical methods are a limiting factor in their use. These methods are especially useful in patients who are at high risk of bleeding. These may also be used in combination with anti-coagulant prophylaxis to improve efficacy.48

Caution: Not to be used in the presence of DVT.
OPINION OF VTE EXPERT GROUP REGARDING SUGGESTIONS FOR PREVENTION AND MANAGEMENT OF VTE 2006

Suggestions

Obstetrics

Incidence in Pregnancy

The incidence of thromboembolic complications in pregnancy is under-estimated and varies between two and five per 1000 deliveries, in published reports.°

Pregnancy and VTE

Venous Thrombosis in Pregnancy

Certain physiological changes of pregnancy which predispose to thrombosis are:

- Increase in several plasma proteins concerned with clotting.
- Increase in levels of fibrinogen, factor VII, VIII and IX.
- Changes in Protein S and Protein C, which are natural inhibitors of blood coagulation.

The pathogenesis of thrombosis in pregnancy is therefore most likely to be a product of the increased tendency to venous thrombosis in lower limbs. This combined with a shift in the balance between coagulation and fibrinolysis, towards enhanced coagulation and diminished fibrinolysis, encourages thrombus growth.

Clinical Features

The normal discomforts of pregnancy can often mimic the symptoms of leg vein thrombosis. Leg cramps, swelling of ankles, slight cyanosis of the legs and an increased prominence of the superficial veins on standing are often seen especially in late pregnancy. Venous Thrombosis when present will almost invariably cause more symptoms in one leg than the other and usually is in the left leg. The diagnosis of DVT is almost certain when physical signs of calf tenderness and induration of calf muscles with unilateral edema and increased skin temperature of the leg are present.

In the early stages, even extensive thrombi are often asymptomatic and their presence may first be suspected with occurrence of Pulmonary Embolism.

The symptoms and signs of PE are predominantly associated with cardiovascular and respiratory systems. The immediate effects vary from clinically silent to sudden death and depend on the condition of the patient and the size of embolus.

The clinical diagnosis of both VTE and PE in pregnancy is subject to error, and whenever possible, objective diagnostic techniques like Duplex Ultrasonography should be used.

Diagnostic Requirements for treatment suggest a combination of clinical and ECG evaluation along with duplex scan. MRA in selected cases can be resorted to in life threatening situations.

Since all hospitals do not have the same facilities and expertise, management of patients with VTE or PE in a specific manner is not possible. The approach should be based on urgency of diagnosis and availability of the diagnostic procedures.

Common Suggestions to the Patient

- Emphasize on pelvic rest (no intercourse) and not absolute bed rest.
- The pregnant woman lying on her back in late pregnancy is likely to aggravate venous stasis in the legs due to the compression of the vena cava. She may be advised to rest on one side and not on her back. Venous return from the lower limbs is encouraged by elevation of the feet by 15 to 20 cm.
- Exercises of the affected leg promote development of collateral venous channels and are likely to be major factors in preventing long term venous insufficiency.
- Early mobilization is mandatory.
- Adequate hydration.

Risk category stratification for obstetric patients is indicated in Table 7.

Suggestions

- All women may undergo an assessment of risk factors for VTE before or in early pregnancy. This assessment may be repeated if the woman is admitted to hospital or develops other intercurrent problems (Grade C).
- Women with previous VTE or a strong family history of VTE may be screened for inherited and

<table>
<thead>
<tr>
<th>Category</th>
<th>Calf Vein Thrombosis (%)</th>
<th>Frequency of Proximal Vein Thrombosis (%)</th>
<th>Fatal PE (%)</th>
<th>Obestrics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>40-80</td>
<td>10-30</td>
<td>&gt;1</td>
<td>History of DVT/PE, Thrombophilia</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>10-40</td>
<td>1-10</td>
<td>0.1-1</td>
<td>Age&gt;40 years</td>
</tr>
<tr>
<td>Low Risk</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>&lt;0.1</td>
<td>Age&lt;40 without any risk factors</td>
</tr>
</tbody>
</table>

*the risk of DVT in obstetric patients with pre-eclampsia and other factors is unknown but prophylaxis should be considered.
acquired thrombophilia ideally before pregnancy (Grade C).

- Regardless of the risk of VTE, immobilization of women during pregnancy, labor and the puerperium should be minimized and dehydration should be avoided. Emphasis is on early ambulation and not bed rest.

- Women, with previous recurrent VTE, or a previous VTE and a family history of VTE in a first degree relative, may be offered thromboprophylaxis with LMWH in antenatal period and for at least 6 weeks postpartum (Grade B).

- For women with recurrent pregnancy loss (three or more miscarriages) and women with prior severe or recurrent pre-eclampsia, abruptions or otherwise unexplained intrauterine death, screening for congenital thrombophilia is suggested.

- Patients with APS and no prior VTE or pregnancy loss may be considered to have an increased risk for development of venous thrombosis and perhaps pregnancy loss. Any one of the following approaches is suggested:
  - Low dose aspirin 75 – 150 mg/day.
  - Surveillance.
  - Prophylactic LMWH.
  - Mini dose of UFH.

- For pregnant patients with antiphospholipid syndrome (APS) and a history of multiple (two or more) early pregnancy losses or one or more late pregnancy losses, pre-eclampsia, intrauterine growth retardation (IUGR) or abortion, administration of ante-partum aspirin plus a mini or a moderate dose UFH or prophylactic LMWH is suggested (Grade B).

- For women who are homozygous for thermo labile variant of MTHFR, folic acid supplement prior to conception or if already pregnant, as soon as possible and throughout pregnancy is suggested.

- For women with congenital thrombophilic deficit and recurrent miscarriages, a second trimester or later loss, severe or recurrent pre-eclampsia or abortion, low dose aspirin therapy plus either mini dose UFH or prophylactic LMWH therapy, antenatal and postpartum for a period of 6 weeks is suggested.

- Women in whom a previous VTE is estrogen related [pregnancy or the Combined Oral Contraceptive (COC)] or additional risk factors such as obesity are present, may be started with thromboprophylaxis with LMWH as early as possible in pregnancy (Grade C).

- Women with three or more persisting risk factors may be considered for thromboprophylaxis with LMWH, antenatal and for 3 to 5 days postpartum.

Women may be reassessed before or during labor for risk factors for VTE. Age over 35 years and BMI greater than 23-25/body weight (greater than 70 kg) are important independent risk factors for postpartum VTE even after vaginal delivery. The combination of either of the risk factors with any other risk factor for VTE, with the presence of two other persisting risk factors may lead clinicians to consider use of LMWH for 3-5 days postpartum.

- For women requiring long term oral anticoagulant therapy who are attempting pregnancy, the group suggested substituting UFH or LMWH for warfarin as soon as pregnancy is achieved.

**Treatment of VTE during pregnancy**

- In women with acute VTE, the group suggests either low dose LMWH throughout pregnancy or intra venous UFH for at least 5 days, followed by adjusted dose of UFH or LMWH for the remainder of pregnancy. Anticoagulants may be administered for at least 6 weeks postpartum.

- In women receiving adjusted dose of LMWH or UFH therapy, heparin may be discontinued 24 hours prior to labor (Grade C).

- Placement of infra-renal IVC filter (preferably retrievable) under duplex sonographic control can be resorted to in dire emergencies.

**In women with prosthetic heart valve, the group suggests**

- Adjusted dose of LMWH 12 hourly throughout pregnancy in doses adjusted either to keep a 4 hour post-injection anti Xa level at approximately 1 to 1.2 u/ml or according to weight.

- Adjusted dose of UFH throughout pregnancy which is administered 12 hourly, in doses adjusted to keep the mid interval aPTT at least twice control.

- UFH or LMWH until the thirteenth week, change to warfarin until the middle of the third trimester and then restart UFH or LMWH (Grade C).

- Long-term anticoagulant may be resumed postpartum with all regimens.

- In women with prosthetic valves at high risk, the group suggests the addition of low dose aspirin, 75 to 150 mg/d.

**Delivery and the Puerperium**

- For delivery by elective caesarean section, the women may receive a thromboprophylactic dose of LMWH on the day before delivery (Grade C).

- On the day of delivery, the thromboprophylactic dose of LMWH may be given three hours postoperatively or 4 hours after removal of the epidural catheter (Grade C).

- Where anticoagulants are contraindicated, GEC stockings may be worn for at least 6 weeks following delivery and may be combined with 75mg of aspirin
Breast feeding is not contraindicated with either LMWH, unfractionated heparin or warfarin (Grade B).

Advice on Preventing DVT for Pregnant Women Traveling by Air

There is no data available to reach an evidence based analysis of the risk of travel related VTE in pregnancy. However, the risk of travelers’ thrombosis is further increased in pregnant women. The risk is greatest in those who have previous history of VTE and/or are suffering from thrombophilia.

The group suggests:
- Calf exercises.
- Ambulation inside aircraft.
- Avoidance of dehydration.
- Pregnant women are suggested to wear properly fitting elastic compression stockings for long travel time (>4 hours duration) flights or for all flights if they have additional risk factors or
- LMWH may be given for pregnant women at increased risk who are taking long flights on the day of travel and the day after.

Hormone Replacement Therapy (HRT) and VTE
- All women commencing Hormone Replacement Therapy (HRT) may be counseled about the risk of VTE. This will make them aware of signs and symptoms of VTE and enable them to access medical help as soon as possible, if they suspect that they have developed thrombosis.
- Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT was suggested inappropriate.
- HRT may be avoided in women with multiple pre-existing risk factors for VTE.
- Selective estrogen receptor modulators may be considered to carry the same risk of thrombosis as estrogen containing HRT.
- HRT may be considered a risk factor for VTE when assessing women pre-operatively. However, HRT does not require to be routinely stopped prior to surgery provided that appropriate thromboprophylaxis such as low dose LMWH, with or without thromboembolic deterrent stocking is given.

**Gynecologic Surgery**

Risk category stratification for gynecology patients is indicated in Table 8.

**Suggestions**

- **Low Risk:** For patients undergoing major gynecological surgery for benign disease without additional risk factors, the group suggests against the use of specific prophylaxis other than early and persistent mobilization and adequate hydration.
- **Moderate Risk:** Thromboprophylaxis with LDUH (5000 units twice a day) or LMWH (according to manufacturer’s instructions), till the patient is ambulatory (Grade A). IPC used continuously may also be considered (Grade A). Adjusted dose warfarin may have a role when low dose heparin is contraindicated, for eg: in HIT, but is not suggested for routine prophylaxis (Grade A).
- **High Risk:** The group suggests LMWH (high risk daily dose as per manufacturer’s instructions) (Grade A), LDUH (5000 units 8 hourly) (Grade A) or IPC (throughout hospital stay) (Grade B) or LMWH or low dose unfractionated heparin (LDUH) + IPC or GEC for optimal prophylaxis (insufficient data available for grading).
- **Higher Risk:** The group suggested continuation of prophylaxis may be continued for 2-4 weeks after hospital discharge (to be decided on individual basis) (Grade C).

**Hematology**

Asymptomatic patients with congenital thrombophilia

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### Table 8: Risk category stratification for gynecology patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Calf Thrombosis (%)</th>
<th>Frequency Of Proximal Vein Thrombosis (%)</th>
<th>Fatal PE (%)</th>
<th>Gynecology</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>40-80</td>
<td>10-30</td>
<td>&gt;1</td>
<td>Major gynecological surgery, age&gt;60* Major gynecological surgery, age 40-60 &amp; cancer or history of DVT/PE, thrombophilia Major gynecological surgery, age 40-60</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>10-40</td>
<td>1-10</td>
<td>0.1-1</td>
<td>Major gynecological surgery, age&lt;40, on estrogen therapy Minor surgery, age &gt;60 Minor gynecological surgery, age&lt;40 without any other risk factors* Minor gynecological surgery, surgery, age 40-60 without any other risk factors*</td>
</tr>
<tr>
<td>Low Risk</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>&lt;0.1</td>
<td>Minor gynecological surgery, age 40-60 &amp; cancer or history of DVT/PE, thrombophilia Major gynecological surgery, age 40-60</td>
</tr>
</tbody>
</table>

*Risk is increased by infectious disease, presence of varicose veins, general immobility. Minor surgery: operations lasting less than 45 minutes. Major surgery: any intra-abdominal operation lasting more than 45 minutes.
do not require thromboprophylaxis as a routine but may be protected during surgery or in presence of any medical condition associated with an increased risk of thrombosis.

Thromboprophylaxis may be done by the following:
- Use of LMWH starting preoperatively and continuing once a day till ambulation.
- UF heparin 5000 U given 1-2 hrs pre-op and then Q8H Q12H post operatively.
- D-dimers done on 7th day (discharge time) and 28th day (review time).

**MEDICAL CONDITIONS**

Risk category stratification for medical patients is indicated in Table 9.

**Suggestions**
- The group suggests prophylaxis with LDUH or LMWH (Grade A) for patients with
  - Acute medical illness.
  - Admitted with congestive cardiac failure or severe respiratory disease.
  - Bed confinement and one or more additional risk factors like Cancer, previous VTE, sepsis, acute neurological disease or inflammatory bowel disease.
  - Alternately, GECs or IPC may be considered in cases of active bleeding or if anticoagulant is contraindicated in patients with risk factors for VTE (Grade C).

**CRITICAL CARE**

**Suggestions**
- LDUH or LMWH for high risk or moderate risk patients (Grade A).
- For patients where anticoagulants are contraindicated, GEC stockings with IPC may be considered as alternatives (Grade C).
- In absence of contraindications, combined LDUH or LMWH with GEC’s/IPC may be advised (Grade C).

**ORTHOPEDIC SURGERY**

**Elective Hip Replacement**

**Suggestions**
- The group suggested routine use of the following:
  1. LMWH.
  2. Fondaparinux.
  3. Adjusted oral anticoagulant therapy.
  4. IPC or FIT with GEC in certain patients with risk of bleeding.
- LMWH – The high risk dose of LMWH may start 12 hours before surgery or 12 to 24 hours after surgery or 4-6 hours after surgery at half dose and then the usual high risk dose the following day (Grade A).
- Fondaparinux – Pentasaccharide, which is an indirect inhibitor of factor Xa, (2.5mg) started 6-8 hours after surgery (Grade A).
- Adjusted dose of oral anticoagulant started pre-operatively or evening after surgery (INR target 2.5 or range 2-3) (Grade A).
- Prophylaxis may be initiated either before or after operation depending upon adopted regime and may be continued 4-6 weeks with LMWH (Grade A) or Pentasaccharide (Grade C).
- Recombinant Hirudin is approved for short-term prophylaxis and may be used in patients with HIT (Grade A).
- The group suggests against the use of Aspirin, Dextran, LDUH, GEC, IPC or venous foot pump (VFP) as the only method of thromboprophylaxis in these patients (Grade A).

**Elective Knee Replacement**

**Suggestions**
- Routine thromboprophylaxis using LMWH or Fondaparinux or adjusted dose VKA (Grade A).
- IPC or foot impulse technology + GEC are an alternative option but more studies are needed (Grade B).
- Use of any sole method of thromboprophylaxis with aspirin, LDUH or Venous Foot Pump is not suggested (Grade A).

**Hip Fracture Surgery (HFS)**

The group suggests the following:

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<table>
<thead>
<tr>
<th>Category</th>
<th>Calf Vein Thrombosis (%)</th>
<th>Frequency Of Proximal Vein Thrombosis (%)</th>
<th>Fatal PE (%)</th>
<th>Medical Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>40-80</td>
<td>10-30</td>
<td>&gt;1</td>
<td>Stroke, Age &gt; 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>10-40</td>
<td>1-10</td>
<td>0.1-1</td>
<td>Shock, History of DVT/PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Low Risk</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>&lt;0.1</td>
<td>Immobilized patient with active disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor medical illness</td>
</tr>
</tbody>
</table>

Table 9: Risk category stratification for medical patients

<table>
<thead>
<tr>
<th>Frequency Of Proximal Vein Thrombosis (%)</th>
<th>Medical Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal PE (%)</td>
<td></td>
</tr>
<tr>
<td>0.1-1</td>
<td>Shock, History of DVT/PE</td>
</tr>
<tr>
<td></td>
<td>Thrombophilia</td>
</tr>
<tr>
<td>&lt;0.1</td>
<td>Immobilized patient with active disease</td>
</tr>
<tr>
<td>&lt;0.1</td>
<td>Minor medical illness</td>
</tr>
</tbody>
</table>
• LMWH (Grade A).
• Fondaparinux (Grade A).
• Adjusted dose VKA (INR range 2-3) (Grade A).
• LDUH (Grade A) (Grade A).
• IPC or FIT + GEC may be used when there are contraindications to anticoagulants (Grade C).
• Aspirin alone was not suggested (Grade A).
• If surgery is likely to be delayed, prophylaxis with LMWH or IPC or FIT plus GEC be initiated during time between hospital admission and surgery (Grade C).

KNEE ARTHROSCOPY
Suggestions
• Routine prophylaxis is not suggested (Grade B).
• High risk or prolonged surgery patients – LMWH may be given and continued until full ambulation (Grade B).

OTHER PROPHYLAXIS ISSUES IN MAJOR ORTHOPEDIC SURGERY
Suggestions
Timing of prophylaxis initiation
• The decision of timing of prophylaxis may be based on efficacy to bleeding tradeoffs for that particular agent. For LMWH, pre operative or post operative initiation, are advised (Grade A).
Duration of prophylaxis
• The group suggested that patient undergoing Total Hip Replacement, Total Knee Arthroplasty or HFS receive prophylaxis with LMWH (using a high risk dose), Fondaparinux (2.5mg OD) or a VKA (target INR range 2-3) for at least 10 days (Grade A).
• Extended prophylaxis may be given for 28 to 35 days after surgery to patients undergoing THR or HFS (Grade A).
• Recommended options for extended prophylaxis in THR:
  • LMWH (Grade A).
  • VKA (Grade A).
  • Fondaparinux (Grade C).
• Recommended options for extended prophylaxis in HFS:
  • Fondaparinux (Grade A).
  • LMWH (Grade C).
  • VKA (Grade C).

ISOLATED LOWER EXTREMITIES INJURIES
Suggestions
• The group did not suggest thromboprophylaxis routinely in patients with isolated lower extremity injuries (Grade A).

MULTIPLE TRAUMAS
Suggestions
• The group suggested that all trauma patients with at least one risk factor for VTE receive thromboprophylaxis, if possible (Grade A).
• They also suggested LMWH, starting as soon as bleeding risk is acceptable (Grade A) or IPC in presence of contraindications to LMWH and continued until full ambulation (Grade B).
• The group suggested against the use of IVC filters as primary prophylaxis in trauma patients (Grade C).
• The group suggested the continuation of thromboprophylaxis until hospital discharge, including the period of inpatient rehabilitation (Grade C). Continuing prophylaxis after hospital discharge with LMWH or a VKA (target INR, 2.5; INR range 2-3) in patients with major impaired mobility was suggested (Grade C).

ACUTE SPINAL CORD INJURIES (SCI)
The group agreed to the following suggestions
• Thromboprophylaxis to be provided to all patients with acute SCI (Grade A).
• Prophylaxis with LMWH in combination with IPC and /or GEC (Grade C).
• IPC and/or GEC is to be used when anticoagulant prophylaxis is contraindicated (Grade C).
• They suggested against the use of LDUH, GEC, or IPC as single prophylaxis modalities (Grade A).
• The also suggested against the use of an IVC filters as primary prophylaxis (Grade A). Prophylaxis may be done only during hospitalization.

GENERAL SURGERY
Risk category stratification for General Surgery patients is indicated in Table 10.
Suggestions
• Low Risk : The group suggested against the use of special prophylaxis other than early and persistent mobilization (Grade C).
• Moderate Risk : LDUH 5000 units commenced pre-operatively and continued twice or thrice daily or, LMWH (according to manufacturer recommendations for moderate risk patients) (Grade A).
• High Risk : LDUH 5000 units commenced pre-operatively and continued post operatively three times a day (Grade A) or LMWH commenced pre-operatively and continued post operatively (According to manufacturer’s recommendations) (Grade A). Both may be combined with mechanical
methods (GEC or IPC) (Grade B).

- IPC with GEC compression may be used as an alternative method for patients at risk for or with active bleeding, until total ambulation (Grade A).

- In selected high risk general surgery patients including those who have undergone major cancer surgery, the group suggested post hospital discharge prophylaxis with LMWH (Table 11). This may be decided on individual basis (Grade A).

- In majority of the studies, the duration of prophylaxis has been 5-7 days but extended prophylaxis may be done for selected patients.

### Urological Surgery

#### Suggestions

- The group suggested routine prophylaxis with LDUH twice or three times daily for patients undergoing major, open urologic procedures (Grade A).

- The group suggested against the use of specific prophylaxis other than early and persistent mobilization for patients undergoing transurethral or other low risk urologic procedures (Grade C).

- For actively bleeding urologic patients or patients at high risk of bleeding, the group suggested the use of GEC and/or IPC at least until bleeding risk decreases (Grade C).

#### Vascular Surgery

#### Suggestions

- In patients undergoing vascular surgery who do not have additional thromboembolic risk factors*, routine use thromboprophylaxis was not suggested (Grade B).

- For patients undergoing major vascular surgical procedures who have additional thromboembolic risk factors*, prophylaxis with LDUH or LMWH (Grade C) may be given.

*: Potential thromboembolic risk factors in vascular surgery include advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma, including possible venous injury.

### IVC Filters

The two major indications of placement of IVC filters are:

---

Table 10: Risk category stratification for general surgery patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Calf Vein Thrombosis (%)</th>
<th>Frequency Of Proximal Vein Thrombosis (%)</th>
<th>Fatal PE (%)</th>
<th>General Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>40-80</td>
<td>10-30</td>
<td>&gt;1</td>
<td>Major general surgery, age &gt; 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major general surgery, age 40-60 &amp; cancer or history of DVT/PE/thrombophilia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major general surgery, age 40-60 without other risk factors*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor surgery, age &gt; 60</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>10-40</td>
<td>1-10</td>
<td>0.1-1</td>
<td>Minor surgery, age 40-60 with history of DVT/PE or on estrogen therapy</td>
</tr>
<tr>
<td>Low Risk</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>&lt;0.1</td>
<td>Major general surgery, age &lt; 40, No other risk factors*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor surgery age 40-60, No other risk factors*</td>
</tr>
</tbody>
</table>

*: The risk is increased by infectious diseases, presence of varicose veins, general immobility. Minor surgery: operations other than abdominal lasting less than 45 minutes. Major surgery: any intra-abdominal operation and all other operations lasting more than 45 minutes.

Table 11: Guidelines for transition for inpatient to outpatient anticoagulation: UFH vs. LMWH

<table>
<thead>
<tr>
<th>Indication</th>
<th>UFH</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE Suspected</td>
<td>Obtain baseline aPTT, PT, CBC</td>
<td>Obtain baseline aPTT, PT, CBC</td>
</tr>
<tr>
<td></td>
<td>Check for contraindications to heparin therapy</td>
<td>Check for contraindications to heparin therapy</td>
</tr>
<tr>
<td></td>
<td>Order imaging study, consider giving</td>
<td>Order imaging study, consider giving</td>
</tr>
<tr>
<td></td>
<td>UFH 5000 IU IV</td>
<td>unfractionated Heparin 5000 IU IV or LMWH</td>
</tr>
<tr>
<td>VTE Confirmed</td>
<td>Re-bolus with UFH 80 IU/kg IV and start maintenance infusion at 18 IU/kg</td>
<td>Continue or start sc enoxaparin according to manufacturer’s prescribing information</td>
</tr>
<tr>
<td></td>
<td>Check aPTT at 6 h to keep aPTT in range that corresponds to a therapeutic blood heparin level</td>
<td>Check platelet count between days 3 and 5</td>
</tr>
<tr>
<td></td>
<td>Check platelet count between days 3 and 5</td>
<td>Educate patient about self injection, side effects and complications, importance of follow-up, etc.</td>
</tr>
<tr>
<td></td>
<td>Start warfarin on day 1 at 5mg and adjust subsequent daily dose according to INR</td>
<td>Continue anti-coagulation for at least 3 months</td>
</tr>
<tr>
<td></td>
<td>Stop heparin therapy after at least 4-5 days of combined therapy when INR is ≥2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-coagulate with warfarin for at least 3 months at an INR of 2.5; range, 2.0 to 3.0 PT 5 prothrombin time</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Hyers TM et al.71
1. Major hemorrhage that precedes anti-coagulation
2. Recurrent PE despite well documented adequate anticoagulation.

An IVC Filter prevents PE, not DVT. Patients with filters after an initial PE are more than twice as likely as non-filter patients to require re-hospitalization for DVT. Therefore, when a filter is inserted, anticoagulants may also be used, whenever possible, to prevent further thrombosis. Some patients have an immediate contraindication to anti-coagulation, but the duration of this contraindication is uncertain. Under these circumstances, placement of a non-retrievable filter may be appropriate.

They can also be used for a few days only because of concern for infection at the insertion site. Retrievable filters can be left in place for 10-14 days or permanently if necessary for a trapped large clot or a persistent contraindication to anti-coagulation.

REGIONAL ANESTHESIA IN THE ANTI-COAGULATED PATIENTS

Suggestions

Combining neuraxial techniques with intra-operative anti-coagulation with heparin during vascular surgery was acceptable to the group with the following cautions:

- The technique in patients with other coagulopathia may be avoided.
- Heparin administration may be delayed for 1 hour after needle placement.
- In-dwelling neuraxial catheters may be removed 2-4 hours after the last heparin dose and the patient’s coagulation status is evaluated; re-heparinization may occur one hour after catheter removal.
- Patient to be monitored post-operatively to provide early detection of motor blockade and use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma may be considered.

Pre-operative LMWH

Patients on pre-operative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, needle placement may occur at least 10-12 hours after LMWH dose.

Post-operative LMWH

- The first dose of LMWH may be administered no earlier than 24 hours (if twice daily dosage), postoperatively, regardless of anesthetic technique and only in presence of adequate surgical hemostasis.
- If OD dosage is to be given, then the first post-operative LMWH may be administered 6-8 hours after surgery.

LAPAROSCOPIC SURGERY

Suggestions

- The group suggested against routine thromboprophylaxis in these patients other than aggressive mobilization (Grade A).
- Those who are having additional risk factors, thromboprophylaxis may be given with LDUH, LMWH, IPC or GECs (Grade C).

NEURO SURGERY

Suggestions

- The group suggested that thromboprophylaxis be routinely used in patients undergoing major neurosurgery (Grade A).
- The group suggested the use of IPC in all patients with or without graduated compression stockings (Grade A). Addition of LMWH is associated with an increase of efficacy (Grade A) but use of LMWH is to be individualized as risk of bleeding is high.

CANCER SURGERY

Risk factors for DVT in patients with cancer:

- Chemotherapy.73
- Hormonal therapy (e.g.: Tamoxifen in women).74,75
- Surgery.76,77
- Immobilization due to prolonged bed rest.78,79
- Previous history of Thromboembolic event.6
- Central venous catheter (CVC).80

Suggestions

- In adult cancer patients who have been admitted or who are confined to bed and have one or more additional risk factors including chemotherapy, or surgery, periods of immobilization, prophylaxis with LDUH or LMWH was suggested (Grade A). Agent selection may be based on renal failure (Cr Cl < 30ml/ml) cost, ease of administration, monitoring and ability to reverse anticoagulation.
- Group suggested appropriate anticoagulation (oral or parenteral) depending on affordability and availability, for the long-term treatment of acute VTE in cancer patients, and may be continued for a minimum of 3-6 months (Grade A).
- In patients who are undergoing major cancer surgery LDUH 5000 units commenced pre-operatively and continued post operatively three times a day (Grade A) or LMWH commenced pre-operatively and continued post operatively (According to manufacturer’s recommendations) (Grade A). Both may be combined with mechanical methods (GEC or IPC) (Grade B). The duration of prophylaxis needs further study.
In patients who have undergone major cancer surgery, the group suggested post hospital discharge prophylaxis with LMWH. This may be decided on individual basis. (Grade A).

The group suggests that clinicians not routinely use prophylaxis for long term indwelling CVC’s in cancer patients (Grade B). It was specifically suggested that clinicians not use LMWH, and fixed dose warfarin (Grade B) for this indication.

**The Relative Contraindications to Anticoagulation Treatment**

- Recent central nervous system (CNS) bleed, intracranial or spinal lesion.
- High risk for bleeding.
- Active bleeding (major): more than 2 units transfused in 24 hours.
- Chronic, clinically significant measurable bleeding > 48 hours.
- Thrombocytopenia (platelets < 50,000/mcL).
- Recent major operation at high risk for bleeding.

**Burns**

**Suggestions**

- The group suggested the use of LMWH (Grade C) as soon as it is considered safe to do so.
- Burn patients with additional risk factors for VTE including one or more of following: advance age, morbid obesity, extensive or lower extremity burns, concomitant lower extremity trauma, use of femoral venous catheter, and /or prolonged immobility may receive thromboprophylaxis, if possible (Grade C).

**Long Distance Travel**

- 10% of air travel passengers older than 50 years develop symptomless DVT during long flights.81,82

**Suggestions**

- The group suggested the following general measures for long distance travelers by air where flight time >6 hours:
  - Avoid tight clothing (Grade C),
  - Avoid dehydration (Grade C), and
  - Perform frequent calf muscle stretching exercises (Grade C).
- For long distance travelers with additional risk factors the group suggested either GEC or a single dose of LMWH injected prior to departure (Grade B).
- The group did not suggest Aspirin for prophylaxis (Grade B).

**Antithrombotic Drugs and Neuraxial Anesthesia**

**Suggestions**

The risk of perispinal epidural hematoma may be increased with concomitant use of antithrombotic drugs while using neuraxial anesthesia or analgesia.

Removal of the epidural catheter, especially in presence of an anticoagulant effect has also been associated with hematoma.

**The Group suggests**

- Removal of epidural catheter when the anticoagulant effect is at its minimum.
- Anticoagulant prophylaxis may be delayed for at least 2 hours after removal of spinal needle or epidural catheter.
- If prophylaxis with a VKA such as warfarin continues, epidural analgesia may not be used for longer than 1 or 2 days (INR should be <1.5 at the time of catheter removal).
- In all patients undergoing neuraxial anesthesia or analgesia, the group suggested special caution when using anticoagulant prophylaxis (Grade C).

**Contraindications to neuraxial anesthesia and analgesia**

<table>
<thead>
<tr>
<th>Prothrombin time (PT)</th>
<th>INR &gt; 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT</td>
<td>&gt;40 s</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt;50,000 L^{-1}</td>
</tr>
</tbody>
</table>

**Unanswered Questions**

1. Published data on the risk of DVT in Indian population is sparse. Incidence and prevalence studies in various sub groups of patients would benefit in defining any alterations needed in the prophylactic methods published in western literature.
2. Need to study the role of D-Dimer and its relationship with occult malignancy in idiopathic DVT.
3. The risk of DVT in minimally invasive surgeries needs to be established.
4. Further studies are needed to assess the additive effects on the efficacy, cost effectiveness and safety of LMWH in high risk patients of various medical and surgical patients.
5. As septic abortions are very common in India, there is a need to study the incidence of thromboembolism in these patients and the need for thromboprophylaxis.
6. Assessment of incidence of thrombophilia in Indian patients.
7. A study on the incidence of thrombosis in HIV positive cases in India could be a topic for future study.
8. Mortality data in high risk categories in Indian
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patients.

9. Due to paucity of Oncology data in Indian context, the group strongly felt the need for appropriate trials to study the following:

a. Duration of post operative prophylaxis
b. The role oral anticoagulants in post op prophylaxis and therapy.

c. To form a registry of assessing relative risk of VTE in different cancer patients.

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Grade A recommendations are based on level 1 evidence from more than one randomised controlled trials that have shown consistent results (e.g., in systematic reviews), and are directly applicable to the target population. High quality and methodologically sound single randomised controlled trials have been classified as grade B.

Grade B recommendations are based on level 1 evidence from randomised controlled trials with less consistent results, limited power, or other methodological problems, or from a different group of patients to the target population.

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Meetings of various specialists in the field of Gastrointestinal Surgery, General and Vascular Surgery, Hematology, Intensive Care, Obstetrics and Gynecology, Oncology and Orthopedics were held in the months of August 2005 to January 2006. The experiences and impressions of the experts during these meetings have been included in this document.

Venous Thromboembolism is an important healthcare problem the world over, resulting in significant morbidity, mortality and resource expenditure. The fact that studies are not available from Indian patients does not necessarily mean that data from the West would not hold for our population. Further, a repetition of the same studies as done in the West would not be needed, and may not throw any new light on the subject.

The implementation of evidence based and thoughtful prophylaxis strategies would be beneficial to the patients in terms of accessing the best possible care. The group felt that every hospital should develop a formal strategy that addresses the prevention of thromboembolic complications. This may be in the form of written guidelines, which are applicable to the needs of the attending patients.

Grades of Recommendations

The grades of recommendations used are those that have been used by the IUA.

Grade A recommendations are based on level 1 evidence from more than one randomised controlled trials that have shown consistent results (e.g., in systematic reviews), and are directly applicable to the target population. High quality and methodologically sound single randomised controlled trials have been classified as grade B.

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