

The hypercoagulable states in anaesthesia and critical care

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ABSTRACT

Hypercoagulable disorders are now diagnosed more frequently than before. These patients are, usually, managed with multiple anticoagulant and antiplatelet medications. Left unmonitored and unevaluated, there can be disastrous haemorrhagic or thrombotic complications. Appropriate perioperative and anaesthetic management of these patients will invite an aetiological diagnosis, severity analysis and the on-going treatment review. Different assays, thromboelastography and molecular cytogenetics have helped to diagnose these conditions precisely and thus guide the long-term management. Besides this, there are varieties of clinical conditions that will predispose to the hypercoagulability. These need to be defined and classified in order to offer a suitable therapeutic option. Pregnancy is one such important condition and can have more than one responsible factor favouring hypercoagulability. With such diverse kinds of disorders, it would be essential to note the anaesthetic implications, to avoid adverse perioperative outcomes. Available evidence based guidelines will help to make the therapeutic approach more precise. Selection of the appropriate technique of anaesthesia, offering the appropriate anticoagulation bridging as necessary and defining an appropriate interval and time for the intervention will help to minimise the complications.

Key words: Anaesthesia, anticoagulants and anaesthesia, clotting, coagulation, critical care, hypercoagulability

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/0019-5049.144682
Quick response code


INTRODUCTION

Hypercoagulable states have been described since 1854 when Rudolph Virchow described a triad of venous stasis, inflammation of or nearby the blood vessels and intrinsic alteration of the blood.^[1-3]

In view of the rise in the patients on various prophylactic and therapeutic anticoagulants and antiplatelet medications coming for surgery, it will be prudent to review the available information to define the management approach in these complex cases.

CLASSIFICATION AND AETIOLOGY

Hypercoagulant states can be classified into three groups, inherited, acquired and others (mixed or unknown). They are seen as either arterial or venous thrombosis, the latter being more common. All the

hypercoagulable states may not clinically present with overt thrombotic episodes, and all the overt thrombotic episodes may not have a presence of a known aetiological factor. This complexity creates a difficulty in diagnosing and treating the hypercoagulability syndromes.

The inherited disorders are due to deficiencies of proteins C, S and antithrombin III. They are found in about 15% cases of venous thrombosis. However, the presence of factor V Leiden (FVL) seems to be the more common aetiological factor in the inherited group. FVL is the result of single point mutation on the gene coding coagulation factor V. This mutation (G1691A), which is autosomal dominant, renders coagulation factor V resistant to inactivation by activated protein C (APC).

Many acquired factors seem to predispose to the hypercoagulable states and are as below.^[4]

How to cite this article: Bande BD, Bande SB, Mohite S. The hypercoagulable states in anaesthesia and critical care. Indian J Anaesth 2014;58:665-71.

Acquired

- Age
- Previous thrombosis
- Immobilization
- Major surgery, orthopaedic surgery
- Malignancy
- Oral contraceptives
- Pregnancy
- Hormonal replacement therapy
- Antiphospholipid syndrome
- Essential thrombocythemia
- Polycythemia vera
- Paroxysmal nocturnal haemoglobinuria
- Splenectomy.

Inherited

- FVL G1691A
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Dysfibrinogenemia
- Prothrombin mutation G20210A.

Mixed or unknown

- Hyperhomocysteinemia
- High levels of factor VIII
- APC-resistance in the absence of FVL
- High levels of factor IX, factor XI and TAFI.

possible to detect many of these previously less known entities. Anaesthesiologists are likely to face these cases more often than before and will need to know more about their perioperative relevance.

PREVALENCE OF HYPERCOAGULABLE STATES

The thermolabile variant of the methylene tetrahydrofolate reductase (MTHFR) gene (C677T) increases the plasma homocysteine levels, and hyperhomocysteinemia is a known risk factor of deep vein thrombosis. FVL mutations are known to potentiate the effect of MTHFR on deep vein thrombosis.

The incidence of FVL mutation was found to be 10% and 20% in Western Indian and American populations, respectively. The incidence of FVL mutation in a cohort of deep vein thrombosis patients was found to be 25% in both these population groups.^[1,5] In western Indian population, 2 out of 4 patients who were positive for both FVL and C677T MTHFR mutations, had poor prognosis and died indicating their fatal synergistic role.^[5]

Pathophysiology

Human haemostasis is a complex phenomenon where a plug formation occurs at the site of injury while the blood is maintained fluid elsewhere thus bringing in interplay of multiple factors and components [Figures 1 and 2].

With advances in laboratory diagnostics, it is now

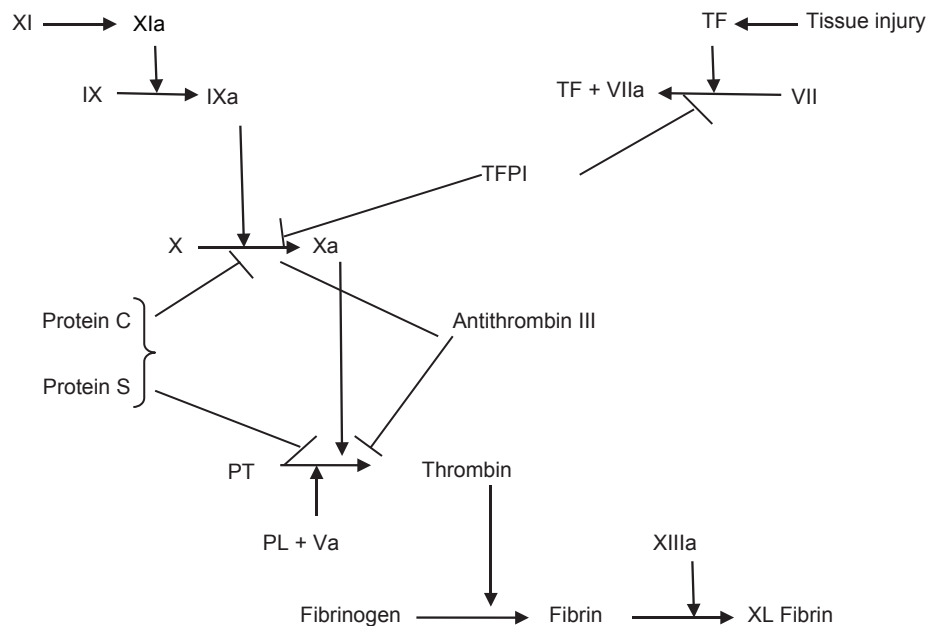


Figure 1: Cross-linked fibrin formation (coagulation cascade) PT–Prothrombin; TF–Tissue factor; TFPI–Tissue factor pathway inhibitor; PL–Phospholipid; XL–Cross-linked. (→ Fascilitation) (—| Inhibition)

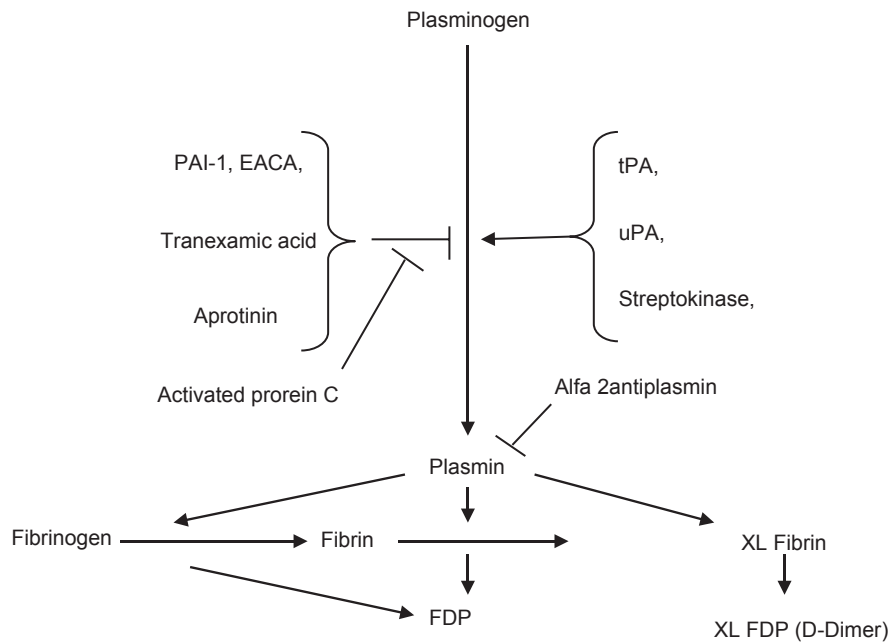


Figure 2: Fibrinolysis PAI-1–Plasminogen activator inhibitor-1; tPA–Tissue plasminogen activator; u-PA–Urokinase plasminogen activator; FDP –Fibrinogen degradation products; XL–Cross-linked. (→Facilitation) (—| Inhibition)

This particular process is triggered, governed and affected by variety of factors. Any alteration in these factors probably leads to an abnormal coagulation process leading to either haemorrhagic or thrombotic events. Hyperfibrinogenemia and thrombocytosis can result as a response to biomaterials, tumours and tissue injury. Chronic exposure to biomaterials can also cause decreased plasminogen activity leading to hypofibrinolysis.^[6]

Diagnosis

Acquired disorders and applicable laboratory tests: Initial tests for all patients are prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), platelet, plasma fibrinogen.

Thromboelastogram (TEG)^[6] can yield some more specific information as to which component is responsible for the hypercoagulability. Besides, TEG can also help in platelet function analysis and mapping. However, its role in predicting perioperative thromboembolic events is found to be limited (62-90% specificity).

For specific aetiological diagnosis one would need following tests^[7]

- APA syndrome (lupus anticoagulant)
 - Tests: 1:1 mix showing inhibitor
 - Hexagonal phase lupus inhibitor assay or dilute Russell viper venom time
 - Anticardiolipin or anti-beta-2-glycoprotein I antibodies by enzyme-linked immunosorbent assay (with titers)

- HIT in appropriate clinical setting
 - HIT Type I-usually clinically mild and non-progressive
 - HIT Type II-acute, severe, progressive, immuno-mediated and may develop life-threatening paradoxical thrombosis
 - Test: Platelet factor IV antibody.

Inherited Disorders and applicable laboratory tests

Initial testing for all patients: PT, aPTT, TT, platelet, fibrinogen

- FVL/APC resistance (most common)
 - Test: aPC resistance assay OR DNA analysis for FVL-both can determine if patient is heterozygote or homozygote
- Factor II (prothrombin G20210) polymorphism
 - Test: Factor II DNA analysis
- Protein C deficiency, protein S deficiency, or antithrombin III deficiency
 - Test together with: Protein C activity, protein S free antigen assay, antithrombin activity assay
- Persistent elevation of factor VIII with normal C-reactive protein (CRP)
 - Test: Factor VIII activity and CRP.

Pregnancy and hypercoagulability

Venous thrombo embolism (VTE) occurs in 10/100,000 women of childbearing age and affects 100/100,000 pregnancies. The risk of pulmonary embolism is increased during pregnancy. There is 20 times higher

incidence of thromboembolism after caesarean delivery when compared to vaginal delivery. VTE is emerging as a leading cause of death peripartum, especially if associated with thrombophilic risk factor. About 50% patients have inherited type of disorders and FVL is the most common among them. Presence of risk factor may require treatment with heparin during pregnancy. Heparin is known to be effective and safe during pregnancy.^[8] The American College of Chest Physicians (ACCP) recommends low molecular weight heparin (LMWH) during pregnancy for the prevention and treatment of VTE, rather than unfractionated heparin or warfarin.^[9] 50% VTE episodes occur postpartum and may necessitate treatment with heparin or warfarin for 6 weeks.^[8]

Treatment

The first episode of the thromboembolic event is treated with anticoagulation therapy followed by thrombophilia screening at the end of the treatment.

There are no specific therapies to reverse most hypercoagulable states. Recombinant factor concentrates of antithrombin and APC exist and may be useful.

Gene transfer to correct a particular genetic defect is theoretically feasible but likely cost prohibitive at this time. Attempts to eliminate APA by plasmapheresis or immunosuppressive therapy have not been very successful.

Hyperhomocysteinemia is treatable, and plasma homocysteine levels can be lowered in many

individuals by folic acid or other B-complex vitamin supplementation.^[10]

Initiation of oral anticoagulation for primary VTE prophylaxis in asymptomatic carriers of any hypercoagulable state has not been advised.

As most VTEs (50-70%) in patients with a predisposition to hypercoagulability occur following a situational risk factor, such as major or orthopaedic surgery, aggressive VTE prophylaxis should be prescribed to asymptomatic carriers of hypercoagulable states during high-risk situations.^[11]

There are currently no data from prospective, randomized, controlled trials specifically designed to address the optimal duration of anticoagulation therapy in patients with specific hypercoagulable states.

The sixth ACCP Guidelines on antithrombotic therapy do not recommend continuation of anticoagulation therapy beyond 3-6 months after a situational VTE in patients with heterozygous FVL or the prothrombin G20210A mutation, and suggest that such therapy should last “1 year to lifetime” only in individuals with active cancer, persistently elevated anticardiolipin antibodies, and antithrombin deficiency.^[12]

ANTICOAGULANTS AND ANAESTHETIC IMPLICATIONS

The chief concerns of patients on anticoagulants are related to haemorrhagic complications when the

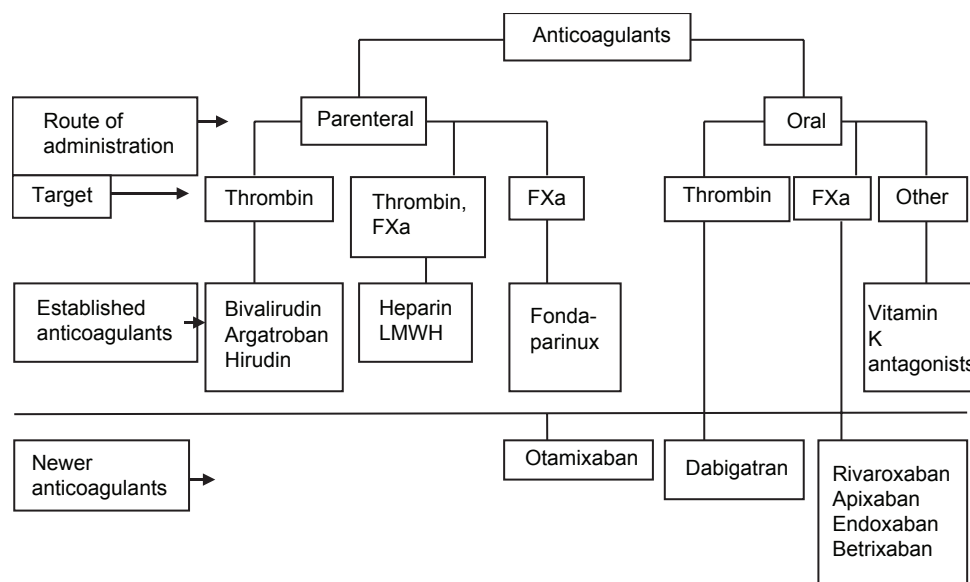


Figure 3: Classification of anticoagulants

patients present for the surgery while they are on prophylactic or therapeutic anticoagulation.

Approved prophylactic regimens for the perioperative setting are (Figure 3^[13]): Unfractionated heparin: 5000 IU s/c, twice daily, Enoxaparin: 40-60 mg s/c once daily, Fondaparinux: 2.5 mg s/c once daily, Rivaroxaban: 10 mg p/o once daily and Dabigatran: 110-220 mg p/o once daily.

DURATION OF PHARMACOLOGIC PROPHYLACTIC ANTICOAGULATION

- 7-10 days or until the patient has regained full ambulatory status
- Operations or contexts associated with a very high or prolonged VTE risk mandate the so-called (>10 days, for up to 35 days) prolonged prophylaxis. Example; hip-fracture surgery, neurosurgery, trauma-surgery and neuro-rehabilitation
- 1 month, for patients with major abdominal and pelvic (including cancer) surgery.

MONITORING OF PROPHYLACTIC ANTICOAGULATION

Low molecular weight heparin, fondaparinux and also the new direct anti-Xa and anti-IIa agents do not require monitoring as they possess the advantage of having a predictable dose-response effect.^[13] If required, anti-Xa activity can be measured. In intensive care unit patients, poor cutaneous circulation and oedema may give unpredictable response.^[14]

IS INTERRUPTION OF ANTITHROMBOTIC THERAPY IN THE PERIOPERATIVE PERIOD NEEDED?

- Yes: In patients who are having a major surgical or other major invasive procedure
- No: In patients who are undergoing minor surgical or invasive procedure (e.g. dental, skin, or cataract).^[15]

PATIENTS WITH CORONARY STENTS

- In patients receiving dual antiplatelet therapy and requiring surgery, defer surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent.
- In patients who require surgery within 6 weeks of placement of a bare-metal stent or within

6 months of placement of a drug-eluting stent, continue dual antiplatelet therapy around the time of surgery.^[15]

WHICH PATIENTS ON WARFARIN SHOULD RECEIVE HEPARIN BRIDGING BEFORE SURGERY?

Elective surgery is postponed if thromboembolism occurred within 1 month. May need consideration for vena cava filter if they need urgent surgery.^{[15][16]}

High risk for thromboembolism: Bridging advised

- Known hypercoagulable state:
 - Protein C deficiency
 - Protein S deficiency
 - Antithrombin III deficiency
 - Homozygous FVL mutation
 - APA syndrome
- Recurrent arterial or idiopathic venous thromboembolic events (excluding primary atherosclerotic events, such as stroke or myocardial infarction due to intrinsic cerebrovascular or coronary disease)
- VTE, 1-3 months.

Intermediate risk: Usually post-operative bridging

- Venous or arterial thromboembolism, 3-6 months ago.

Low risk for thromboembolism: Bridging not advised

- One remote VTE (>6 months ago).

PROTOCOL FOR HEPARIN BRIDGING THERAPY

Before surgery

- If pre-operative international normalized ratio (INR) is 2.0-3.0, stop warfarin 5 days before surgery (i.e. hold four doses)
- If pre-operative INR is 3-4.5, stop warfarin 6 days before surgery (hold five doses)
- Start LMWH 36 h after last warfarin dose, that is, Enoxaparin 1 mg/kg subcutaneously every 12 h or Enoxaparin 1.5 mg/kg subcutaneously every 24 h
- Give last dose of LMWH approximately 24 h before procedure
- Check INR in morning of surgery to ensure that it is <1.5, or in some cases (e.g. neurologic surgery) <1.2
- After surgery, restart enoxaparin 24 h after procedure, after discussing with surgeon

- Start warfarin at patient's pre-operative dose on post-operative day 1
- Daily PT and INR until patient is discharged and periodically thereafter until INR is in the therapeutic range
- Complete blood cell count with platelets on day 3 and day 7
- Discontinue LMWH when INR is 2-3 for 2 consecutive days.

Choice between unfractionated heparin and low molecular weight heparin

The latter can be given on outpatient department basis and is supposed to be safer.

Bridging in the patients with history of heparin-induced thrombocytopenia

Danaparoid or intravenous (i.v.) direct thrombin inhibitors, or perhaps fondaparinux.^[15-16]

REGIONAL ANAESTHETIC MANAGEMENT OF THE PATIENT RECEIVING UNFRACTIONATED HEPARIN

- Delay i.v. heparin administration for 1 h after needle/catheter placement
- Prolonged anticoagulation appears to increase risk of spinal haematoma formation, especially if combined with other anticoagulants or thrombolytics
- If systematic anticoagulation therapy is begun with an epidural catheter in place, delay catheter removal for 2-4 h after heparin discontinuation and after evaluation of coagulation status
- Remove indwelling catheters 1 h before a subsequent heparin administration
- There is no contraindication to the use of neuraxial techniques during subcutaneous standard heparin at total doses, 10,000 units daily
- Assess on an individual basis and implement more frequent neurological monitoring
- Serial platelet counts are indicated for patients receiving subcutaneous heparin for 5 days.

A total of 30 cases of spinal haematoma in patients undergoing spinal or epidural anaesthesia while receiving LMWH perioperatively were reported between May 1993 and November 1997.^[6]

PRECAUTIONS WITH EPIDURAL CATHETERS WHEN USING LOW-MOLECULAR-WEIGHT HEPARINS

- No co-administration of antiplatelet or oral anticoagulant medications

- Lumbar puncture should be delayed at least 12 h after the last thromboprophylactic dose and at least 24 h in case of therapeutic doses
- Post-operatively, the first dose should be given no earlier than 24 h after surgery
- In general, the epidural catheter should be removed about 12 h after the last prophylactic dose
- The first dose of a LMWH should be given no earlier than 2 h after the catheter is removed
- Concurrent use of a LMWH in therapeutic doses and indwelling epidural catheter is generally not recommended
- LMWH use should be delayed for 24 h if the patient experienced excessive trauma to the epidural space during attempted epidural or spinal anaesthesia.^[16]

Antiplatelet drugs

A prospective study involving 1000 patients reported that trauma incurred during needle or catheter placement neither increased nor was sustained by these medications.^[17]

REGIONAL ANAESTHETIC MANAGEMENT OF THE PATIENT RECEIVING ANTIPLATELET MEDICATIONS

- The decision to perform a neuraxial block on a patient receiving perioperative (anticoagulation) must be made on an individual basis by weighing the risk of spinal haematoma with the benefits of regional anaesthesia for a particular patient
- Administration of the anticoagulant, antiplatelet and fibrinolytic agents should be avoided during the period when neuraxial catheter is *in situ*.

The details of all these drugs and the relevant time durations are given in the Table 1.^[17-19]

SUMMARY

Hypercoagulability is an important perioperative concern as its prevalence is on the rise. Specific diagnosis can be difficult. It needs appropriate management approach perioperatively. Bleeding and neuraxial haematomas can be disastrous complications at times. Associated low platelet count may need modification in the anticoagulant doses. Available evidence based guidelines will help to offer more precise therapeutic options. TEG data analysis may add to the

Table 1: Neuraxial anaesthesia and antiplatelets, anticoagulants, and fibrinolytic drugs

Antiplatelet/ anticoagulant drug	Discontinuation period before neuraxial blockade	Waiting period to restart the drug after neuraxial blockade and insertion/ removal of epidural catheter
Aspirin	Not to discontinue	-
Dipyridamole	24 h	2 h
Ticlopidine	14 days	2 h
Clopidogrel	7 days	2 h
Prasugrel	10 days	6 h
Ticagrelor	5 days	6 h
Cilostazol	42 h	5 h (more in renal impairment)
Tirofiban	8 h	2 h
Eptafibatide	8 h	2 h
Abciximab	48 h	2 h
Warfarin	5 days	24 h
Dabigatran	3 days	6 h (24 h in traumatic punctures)
Argatroban	aPTT<40	2 h
Bivalirudin	aPTT<40	2 h
Lepirudin	aPTT<40	2 h
Rivaroxaban	24 h	6 h (24 h in traumatic punctures)
Apixaban	48 h	6 h (24 h in traumatic punctures)
UFH	6 h	1 h
LMWH	24 h (previously 12 h)	24 h
Fondaparinux	36 h	12 h
Fibrinolytics	10 days	10 days
Streptokinase, alteplase, reteplase, tenecteplase		

aPTT – Activated partial thromboplastin time; LMWH – Low molecular weight heparin; UFH – Un fractionated heparin

specific functional correction in future. Evidence based guidelines need to be followed when neuraxial blockade is planned in the patients on anticoagulation therapy.

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Source of Support: Nil, **Conflict of Interest:** None declared