Peri-operative management of patients on anti-platelet agents and anti-coagulants and prophylaxis for venous thrombo-embolism in the neurosurgical setting – summary of evidence and practice guidelines

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**Introduction**

Several medical conditions mandate the chronic use of anti-haemostatic agents (AHAs), be they anti-platelet agents (APAs), or anti-coagulants (ACAs). AHAs are double-edged swords in the neurosurgical setting, and very careful titration needs to be achieved between the thrombotic risk of the underlying condition, and the haemorrhagic risk of AHA usage. Possibly the most dreaded complication of long term AHA use is intracerebral haemorrhage (ICH). Several questions arise regarding the optimization of the haemostatic system prior to surgery, viz, the risks of intra- and post-operative bleeding if this is not done, the risks of thrombotic complications if AHAs are withdrawn, the need for bridging therapy, etc. Most centres do not have standard policies regarding these issues. A survey carried out across German neurosurgical centres revealed that less than a third had clear policies regarding the management of a patient on AHAs. The peri-operative management of ACAs and APAs varied widely among different centres; for example, in the group of patients at high risk for venous thrombo-embolism (VTE), acetylsalicylic acid (ASA) was discontinued in 22%, bridged in 35%, and continued in 35% of centres.\(^1\)

On the other hand, several neurosurgical patients develop diseases that cause paresis or palsy of one or more limbs, leading to limitation of function and mobility. Such patients are at risk for VTE. Patients with malignant gliomas are also at a particularly high risk for VTE.\(^2\) Therefore, such patients may need pharmacologic prophylaxis for VTE prevention. This needs to be weighed against the risk of haemorrhagic complications, especially in the peri-operative period.\(^3\)

In this article, we discuss the following topics –

1. The basic physiology of the haemostatic pathways and the basic pharmacology of the AHAs
2. Laboratory investigations for patients on AHAs prior to surgery
3. Optimization of patients on AHAs in emergency settings
4. Optimization of patients on AHAs prior to elective surgery
5. Restitution of AHA therapy in the post-operative period
6. VTE prophylaxis in neurosurgical patients

**1. The Basics – Physiology of the haemostatic system and pharmacology of the anti-haemostatic drugs**

For ease of description, the haemostatic process is divided into 3 stages.

**Primary haemostasis**

1. Primary haemostasis refers to the sequence of events involved in formation of the temporary platelet plug after endothelial injury.\(^4,5\) This occurs in three steps– Platelet adhesion- The Gp 1b-IX-V receptor complex present on the platelet surface binds to the subendothelial matrix proteins following endothelial injury, via the von Willebrand factor, which is secreted by injured endothelial cells. Integrins present on platelet surface also adhere directly to the collagen present in subendothelial matrix

2. Platelet activation- Adhesion causes the platelets to change shape and degranulate, releasing alpha and delta granules. ADP, present in the delta granules, binds to the P2Y12 receptor on the surface of platelets and promotes further platelet activation. P2Y12 receptors antagonists such as Clopidogrel, Prasugrel, Ticlopidine, Ticagrelor and Cangrelor exert antiplatelet activity by inhibiting ADP mediated activation [Table 1]

Adhesion also results in activation of phospholipase A\(_2\) enzyme which hydrolyses membrane phospholipids to form arachidonic acid. Cyclooxygenase-1 (COX-1) acts on arachidonic acid to produce thromboxane A\(_2\), a potent platelet aggregator. COX-1 is inhibited by aspirin and other NSAIDS [Table 1]

3. Platelet aggregation- This is mediated by fibrinogen, which forms a cross linked platelet plug by attaching to the fibrinogen receptor Gp IIb/IIIa on multiple platelet surfaces. Gp IIb/IIIa inhibitors include Abciximab, Tirofiban and Eptifibatide. Phosphodiesterase-3 inhibitors such as Dipyridamole and Cilostazol also prevent platelet aggregation by increasing the levels of cAMP and blunting the response to ADP [Table 1].
Another class of drugs, PAR-1 (Protease activated receptor-1) antagonists inhibit thrombin mediated platelet aggregation. Unlike other drugs, they do not affect ADP mediated platelet aggregation or coagulation parameters.\textsuperscript{[6,7]}

**Secondary hemostasis and the coagulation cascade**

The release of tissue factor from the injured endothelium sets off a cascade of events resulting in the formation of a fibrin clot. [Figure 1] The cascade proceeds along two pathways, extrinsic and intrinsic, both resulting in the activation of Factor X, which subsequently activates prothrombin, resulting in formation of fibrin from fibrinogen (common final pathway).\textsuperscript{[8,9]} While the extrinsic and intrinsic pathways allow for better understanding, they are not mutually exclusive and occur simultaneously in vivo.\textsuperscript{[10]}

**Tertiary hemostasis**

Tertiary haemostasis begins when Factor XIIIa causes cross-linking of adjacent fibrin monomers forming a polyfibrin meshwork. This increases the strength of the thrombus and prevents short term dissolution.\textsuperscript{[8]} Fibrinolytics are a class of drugs that activate plasminogen to form plasmin, which lyses the thrombus [Table 2].

**2. Laboratory investigation of patients on AHAs prior to surgery**

**Sample collection**

Laboratory tests of coagulation require citrated plasma derived from whole blood. If the sample is drawn from an indwelling venous catheter, it should be non-heparinized and
have been indwelling for less than 30 minutes. The sample is collected in polypropylene or siliconized glass tubes containing 3.2% sodium citrate in a ratio of 9:1 (9 parts blood and 1 part anticoagulant). Frothing should be prevented while transferring the sample to the tube by allowing it to run down the sides gently. Underfilling of the capillary tube can result in over-citration of plasma, causing chelation of exogenous calcium ions and falsely prolonged PT or aPTT. A similar phenomenon can also occur in patients with high haematocrit due to a reduction in the amount of plasma extracted per unit blood volume.

**Tests of coagulation**

While practices differ between centres, the initial battery of coagulation tests is aimed at identifying platelet insufficiency or defects in the extrinsic, intrinsic and final common pathways of the coagulation cascade. These generally include platelet count, bleeding time (BT), clotting time (CT), prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and serum fibrinogen levels. Further evaluation using more specific tests can be done to identify the precise abnormality. A structured approach to diagnosis has been shown to be more cost effective than a shotgun approach.

1. **Bleeding time (BT)** and **Clotting time (CT)**. Bleeding time measures the time taken from infliction of a wound to the arrest of bleeding. (Normal range 2-5 min) It largely reflects platelet function and number, and is independent of the fibrin forming coagulation pathways. Clotting time is the time taken by a sample of blood to coagulate *in vitro* under standard conditions. (Normal range 8-15 min) While they have traditionally been used as screening tests for hemostatic disorders, it has been shown that BT and CT results are abnormal only in severe disease and do not correlate with intraoperative bleeding. Moreover, the lack of standardization of test parameters and multiple confounding factors have rendered these tests unreliable.
2. Prothrombin time (PT). PT is a measure of the extrinsic pathway. The normal range for the PT is 11-15s. While a normal PT indicates adequate levels of Factors VII and X, prolongation may occur as a result of deficiencies in Factors VII and X (extrinsic pathway), factor V, prothrombin or fibrinogen (common final pathway)[8,10]. International Normalized Ratio (INR). Different laboratories use thromboplastins derived from various sources for performing PT. In order to standardize values across laboratories, the sensitivity of thromboplastin is compared to WHO standardized thromboplastin, which is labelled with an International Sensitivity Index (ISI) of 1.0. The INR of a sample represents the PT ratio that would be obtained if the international reference thromboplastin had been used to test the patient. INR = (patient PT in seconds/mean normal PT in seconds)[9].

3. Activated Partial Thromboplastin Time (aPTT). aPTT is the time required for plasma to clot when maximal surface contact activation and optimal phospholipid and calcium concentration are provided.[8,10] (Normal range 35-45s) Prolongation of aPTT reflects an abnormality of both direct and common pathways of the coagulation cascade i.e., Factors I, II, V, X, VII, IX, XI, XII, prekallikrein or HMW-kininogen.

4. Thrombin Time (TT). TT is the time required for formation of a stable clot after addition of thrombin to citrated plasma. (Normal range 12-14s) It measures the ability of fibrinogen to form fibrin strands in vitro.[9] Increased TT is seen in fibrinogen deficiency (congenital or acquired) and in the presence of Heparin.

5. Mixing studies. Prolongation of PT or aPTT can occur either due to deficiency of coagulation factors or due to presence of inhibitors in serum. In presence of an abnormally prolonged PT or aPTT, a mixing study of the specimen can be performed by adding an equal volume of the patient’s citrated plasma to normal pooled plasma.[8] If the abnormal value normalizes after mixing, it indicates clotting factor deficiency in the plasma. Persistent prolongation of PT or aPTT after mixing suggest presence of inhibitors in the plasma.

6. Special coagulation studies
   a. Factor activity assays
   b. Assays for factor inhibitors
   c. Platelet aggregation tests
   d. Specific tests for von Willebrand disease- Platelet function analysis, vWF antigen determination, vWF activity determination using ristocetin cofactor activity), vWF multimer analysis, Ristocetin induced platelet aggregation
   e. Lupus anticoagulant testing- e.g, dilute Russell viper venom time.

3. Optimization of patients on AHAs – emergency situations

The management of a neurosurgical patient on an AHA in an emergency setting can be fraught with difficulty. The lesion and the risk of the patient for VTE (and thus, the indication for AHA therapy), will determine the approach to optimization. If a patient does not require emergent surgery, is at high risk for VTE (see below) and the intracranial lesions are very small, such as a small speck of contusion or a tiny basal ganglionic ICH, then expectant management without disrupting the AHA dosing schedule is a reasonable strategy. On the other hand, larger bleeds, even if managed conservatively, require that the effects of the AHA be reversed. Patients who require emergent surgery must be managed aggressively to normalize the haemostatic system. It should be noted that for antiplatelet induced ICH, routine use of platelet transfusions in conservatively managed patients is not recommended, has been shown to do more harm than good.[15] Platelet transfusions may be used judiciously if the platelet count is <50,000/cc, or as timed infusions during surgery if required.[16]

Emergency situations – APA reversal

Patients with lesions that necessitate acute neurosurgical intervention as well as those with post-traumatic or other spontaneous ICH not requiring surgical evacuation form relative indications for APA reversal, with some authors advocating for reversal in all cases of ICH.[17-19] This, however, remains a point of debate among clinicians, as some trauma literature opposes platelet transfusions to reverse APA action.[18,20,21] The only approved and effective mode of reversal of APA action when necessary, is to transfuse platelets.[18,22,23] Single donor platelets may be better than pooled platelets for the quick reversal of APAs. In high-risk cases, such as an expanding ICH, concurrent administration of 0.3 μg/kg DDAVP (1-desamino-8- D-arginine vasopressin) with platelet transfusion
can be used to achieve maximal and quick platelet activation.[19] There is some literature to support continued platelet transfusions every 12 hours for the first 48 hours after the ictus/injury until physiologic turnover of the platelet pool has occurred.[18,19] While platelet transfusion can successfully reverse the effects of aspirin, for the drugs with longer half-lives and active metabolites like clopidogrel, platelet transfusion is not as reliable. Multiple platelet transfusions for a prolonged period of time may be required to achieve adequate clotting. Activated factor VII can be used in life threatening emergencies, especially in the setting of dual antiplatelet therapy. However, the risk of thrombotic complications should be taken into account.

Emergency situations – ACA reversal
Since there are few established guidelines for the reversal of ACAs, the available options should be tailored for any given patient and situation. Vitamin K and fresh frozen plasma (FFP) have been the mainstay for the reversal of warfarin. Reversal by vitamin K alone occurs in a delayed manner (4-6 hours). Additional supplementation with prothrombin complex concentrate (PCC) may be given for rapid reversal in major haemorrhage. Unfractionated heparin (UFH) is effectively reversed by protamine at a dose of 1 mg per 100 units of UFH. Low molecular weight heparins (LWMH) are more resistant to protamine, and undergo only about 50% reversal of action.

Multiple other tailored options are now available for the reversal of AHAs. [Table 2] These newer agents often require to be used in conjunction with FFP. FFP is particularly rich in clotting factors II, V, VII, IX, X, and XI. It is more effective in overcoming the effects of warfarin and factor X inhibitors than in combating bleeding due to factor VIII deficiency.[23] Activated factor VII restores the catalyst necessary to drive activation of factors V and X, with resultant completion of the clotting cascade. It has a short onset of action but requires concomitant administration of FFP.[21,24] PCCs are targeted reversal agents comprised mainly of concentrated factors II, IX, and X with variable amounts of activated factor VII. Standard PCC and derivatives with high concentrations of activated factor VII (KCentral) are most useful in emergent scenarios.[25,26] Clinical studies have shown these agents to have a reversal time over four times faster than that of FFP, though laboratory monitoring of reversal and the duration of their effect have not been definitively determined. Factor VIII Inhibitor Bypassing Activity (FEIBA) is the newest novel agent; it consists of factors II, IX, X (mainly non-activated), and VIIa (mainly activated) in addition to 1–6 units of FVIII coagulation antigen (FVIIIic: Ag) per ml. All patients undergoing anticoagulant reversal have a tangible, if undefined, increase in risk of thrombosis in the postoperative period as well.[24]

Patients on novel anticoagulants are more difficult to manage since tailored reversal agents are not readily available. There has been some experience with factor VIIa and PCCs allowing early intervention with a low incidence of haemorrhagic complications.[26] FFP can and often should be co-administered at the discretion of the provider. The availability of specific reversal agents for some of the novel ACAs is adding to their safety profile - idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban. [Table 2] These drugs are not freely available at the present time in India. Haemodialysis is effective only for dabigatran as other agents are highly protein bound. Activated charcoal is effective if given within 2 hours of ingestion of the drug.

4. Optimization of patients on AHAs for elective neurosurgery
The reversal of APAs and ACAs for elective neurosurgical procedures can be a more methodical and planned process. The safe reversal of APAs rarely requires anything more than withholding the medication preoperatively (5 days for aspirin and 7-10 days for clopidogrel).[21] Warfarin is also typically withheld for 5 days pre-operatively. The novel anticoagulants, although difficult to reverse in the emergent setting, all have relatively short half-lives and are easily reversed by merely waiting. Renal dysfunction is the only major comorbidity to significantly impair and delay clearance of these drugs. In healthy individuals with a creatinine clearance >50 ml/min, the clotting cascade returns to normal within 1–2 days. When creatinine clearance is <50 ml/min, a coagulopathic state can persist for up to 5 days.[21]
### Table 2: Anticoagulant drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Monitoring</th>
<th>Uses</th>
<th>Adverse effects</th>
<th>Reversal agent</th>
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<tbody>
<tr>
<td><strong>HEPARINS</strong></td>
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<tr>
<td>Unfractionated Heparin</td>
<td>Parenteral</td>
<td>aPTT</td>
<td>VTE prophylaxis and treatment, DVT prophylaxis, ACS, Bridge therapy for AF</td>
<td>Hemorrhage, HIT, Hypersensitivity reaction</td>
<td>Protamine sulphate</td>
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<tr>
<td>Dalteparin (LMWH)</td>
<td>Parenteral</td>
<td>Anti-Factor Xa</td>
<td>VTE prophylaxis and treatment, DVT prophylaxis, ACS</td>
<td>Hemorrhage, HIT, Protamine sulphate</td>
<td>Protamine sulphate</td>
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<tr>
<td>Enoxaparin (LMWH)</td>
<td>Parenteral</td>
<td>Anti-Factor Xa</td>
<td>VTE prophylaxis and treatment, DVT prophylaxis, ACS, Bridge therapy for AF</td>
<td>Hemorrhage, HIT, Protamine sulphate</td>
<td>Protamine sulphate</td>
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<tr>
<td>Tinzaparin (LMWH)</td>
<td>Parenteral</td>
<td>Anti-Factor Xa</td>
<td>Treatment of DVT</td>
<td>Hemorrhage, HIT, Protamine sulphate</td>
<td>Protamine sulphate</td>
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<tr>
<td><strong>VITAMIN K ANTAGONISTS</strong></td>
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<td>Warfarin</td>
<td>Oral</td>
<td>PT, INR</td>
<td>Treatment of VTE, AF, post-myocardial infarction, Mechanical/ prosthetic valve replacement</td>
<td>Hemorrhage, Skin necrosis, purple toe syndrome, Teratogenicity, Osteoporosis, Agranulocytosis</td>
<td>Vitamin K, FFP, PCC</td>
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<td><strong>FACTOR Xa INHIBITORS</strong></td>
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<tr>
<td>Fondaparinux</td>
<td>Parenteral</td>
<td>Anti-Factor Xa</td>
<td>VTE prophylaxis and treatment, treatment of STEMI and NSTEMI</td>
<td>Hemorrhage, skin rashes</td>
<td>Four complex PCC</td>
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<tr>
<td>Rivaroxaban</td>
<td>Oral</td>
<td>Anti-Factor Xa</td>
<td>VTE prophylaxis and treatment, stroke prophylaxis in non-valvular AF</td>
<td>Hemorrhage</td>
<td>Four complex PCC</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Oral</td>
<td>Anti-Factor Xa</td>
<td>Stroke, embolism prophylaxis in non-valvular AF</td>
<td>Hemorrhage</td>
<td>Andexanet alfa, Four complex PCC</td>
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<td><strong>DIRECT THROMBIN INHIBITORS</strong></td>
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<td>Dabigatran</td>
<td>Oral</td>
<td>Thrombin time</td>
<td>Stroke, embolism prophylaxis in non-valvular AF</td>
<td>Hemorrhage</td>
<td>Idarucizumab, Four complex PCC</td>
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<tr>
<td>Bivalirudin</td>
<td>Parenteral</td>
<td>Thrombin time</td>
<td>Treatment of ACS, Treatment and prophylaxis of HIT, PCI</td>
<td>Hemorrhage, renal dysfunction</td>
<td>Four complex PCC</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Parenteral</td>
<td>Thrombin time</td>
<td>Treatment and prophylaxis of HIT, PCI</td>
<td>Hemorrhage, hepatic dysfunction</td>
<td>Four complex PCC</td>
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<tr>
<td><strong>FIBRINOLYTICS</strong></td>
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<tr>
<td>Alteplase</td>
<td>Parenteral</td>
<td>PT, aPTT, fibrinogen</td>
<td>STEMI, Massive pulmonary embolism, Acute ischemic stroke</td>
<td>Hemorrhage</td>
<td>Aminocaproic acid, Tranexamic acid</td>
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Perioperative bridging of anticoagulation

In a number of situations, the risk of thromboembolic events precludes full anticoagulant reversal for more than the immediate perioperative period. This category includes:

- Patients with mechanical heart valve (mitral = highest risk)
- Rheumatic heart disease
- Atrial fibrillation (AF) with a CHADS2 score ≥3
- Left atrial thrombus
- Left atrial assist device
- Stroke within 3 months, especially with AF
- Active cancer
- VTE within 6 months
- VTE with severe thrombophilia
- Lupus
- Anti-thrombin III deficiency

These patients carry a high (10%–20%) risk of VTE compared to their age-matched counterparts. In emergency scenarios, the need for urgent intervention often overrides all considerations of embolic sequelae. However, when considering these patients for elective operations, bridging with an easily reversible ACA is often required. Despite the best planning, this patient population carries a higher risk of haemorrhagic complications when a bridge is used (5.0% vs 1.3% with no bridge therapy).

Current opinion holds that patients in all risk groups should stop warfarin 5 days prior to surgery. Patients at a low risk for haemorrhagic complications resulting from the neuurosurgical procedure can begin bridging therapy with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at 36 hours after the last dose of warfarin. Patients at a high risk for haemorrhagic complications should be kept off of all medications for 48–72 hours before instituting a similar bridge. Each group receives the last infusion 6-12 hours before surgery, and a half dose is recommended for patients on LMWH. The preferred bridging agent has long been UFH, though recently LMWH is gaining in popularity due to convenience and decreased overall cost. LMWH can be used safely in the outpatient setting, benefitting patients and providers. When a proper bridge protocol is followed, the rate of peri-operative haemorrhage should be ≤5%. These patients would also benefit from aggressive non-pharmacologic methods to prevent VTE during the ACA holiday period, utilizing all the available clinical options—early ambulation, compression stockings, and sequential compression devices.

5. Restitution of AHA therapy in the post-operative period

The suspension of anticoagulation before surgery and its subsequent reinstitution is a source of great debate in neurosurgery which involves a delicate balance that takes into account the daily risk of thromboembolism—stroke and VTE versus the potentially severe consequences of a postoperative haematoma in the central nervous system (CNS), and wound healing complications that can delay other treatments (e.g., adjuvant radiation therapy for malignant brain tumours). Neurosurgical patients often harbour disease
processes that increase the risk of VTE (i.e., CNS malignancy, hemiparesis from stroke, morbid obesity, and HTN), and this, coupled with a pre-existing reason for systemic anticoagulation raises the stakes even higher.

The RELY trial calculated the perioperative thromboembolic risk for patients with AF to be around 1.2 percent based on a composite endpoint of stroke, cardiovascular death, and pulmonary embolus. In patients with mechanical heart valves, the risk of VTE is roughly 8% if they are given no anticoagulants in perioperative period. In case of a recent VTE (<3 months ago), the incidence of recurrent VTE is as high as 50% in peri-operative period without anticoagulants. There is much anxiety among neurosurgeons regarding direct thrombin inhibitors, due to the current inability to reverse these drugs in the case of severe life-threatening bleeding (i.e., ICH).

Three special situations deserve mention in the context of restitution of AHA therapy—
1. Non-haemorrhagic stroke. If a decompressive craniectomy is indicated in these patients, an attempt should be carried out to perform the surgery without reversal of APAs. If, however, the patient is on ACAs prior to surgery, this would need to be reversed. We tend to restart APAs after a post-operative CT scan as early as 12 hours after surgery
2. Cortical venous/venous sinus thrombosis. Several of these patients require decompressive craniectomy. If the patient is not already on heparin, the surgery can proceed without any extra considerations. If the patient is on heparin (as is usually the case), and requires emergency surgery, we reverse the AHA action with protamine if UFH was the agent. If the patient was on LMW heparin, we administer FFP and continue FFP infusion during surgery. A post-operative CT scan is performed 24 hours after surgery and heparin therapy is resumed 48-72 hours after surgery
3. Moyamoya disease. These patients are almost always on aspirin therapy. Aspirin should not be stopped prior to surgery, and indeed, should even be administered on the morning of surgery, in order to reduce the risk of stroke in these patients.

Reinstitution of heparin and warfarin
The anticoagulant effect of warfarin is not immediate and during the early time-window, warfarin appears to exert a pro-coagulant effect. This is mediated by a rapid decrease in protein C levels outpacing the diminution of factors II and X during the initial 48 hrs of warfarin administration. This change in the coagulation cascade and the potential for a transient period of relative hypercoagulability underlies the recommendation for initial use of heparin or LMWHs during the institution of warfarin therapy. There is no evidence that this strategy is either safe or effective for neurosurgical patients. The prospective peri-operative enoxaparin cohort trial (PROSPECT) recommended that after major cranial and spinal surgery, re-institution of a therapeutic dose of UFH or LMWH should be delayed for 48 to 72 hours after haemostasis has been secured. Very rarely is full anticoagulation started within 24 hours of a neurosurgical procedure. Patients with mechanical heart valves should resume their anticoagulation regimen earlier than a patient with paroxysmal AF or VTE, owing to the higher thromboembolic risk.

Reinstitution of antiplatelet agents
ASA and thienopyridines (ticlopidine, clopidogrel, prasugrel) exhibit an antiplatelet effect within hours of administration, if given in a loading dose. A gradual antiplatelet effect, therefore, is achieved with reinstitution of daily clopidogrel dosing without an oral load, 48 hours after a neurosurgical procedure. It should be noted that while this make some sense as a “middle ground” for neurosurgeons, there is no high-level evidence that such a practice is either safe or effective.

Reinstitution of new oral anticoagulants
Rivaroxaban has a rapid onset and short half-life. The peak plasma concentration is achieved within 2–4 hours after a single dose, which is similar to the onset of LMWHs. Institution of this medication should not begin until the judgment of the neurosurgeon is that bleeding risk is low enough to commit to full anticoagulation, which is generally 2 to 3 days after major cranial and spine surgeries. Apixaban reaches a maximum plasma concentration in an average of 3 hrs after administration of a 20 mg dose. The half-life, route of excretion, and use in renally impaired patients are similar to that of rivaroxaban. It is recommended to delay apixaban for two to three days after major craniospinal procedures, and if needed to use prophylactic dose of LMW heparin during
this period. Dabigatran is the only direct thrombin inhibitor that is used for long-term anticoagulation.\(^{[34]}\) The maximal anticoagulant effect is achieved in 2–3 hrs, with half-life measured at 14–17 hours in patients with normal renal function. It is recommended to delay Dabigatran for 2-3 days after major craniospinal procedures, and if needed to use prophylactic dose LMW heparin for this period.\(^{[35]}\)

### Re-initiation of ACAs and APAs after ICH

Until 2015, literature was skewed against the re-initiation of ACAs in patients with non-valvular AF, certainly after lobar ICH, and preferably also after deep ICH.\(^{[15,36]}\) More recently, studies published in 2017 and later, including the ACC guideline update, have tilted the weight in favour of re-initiation of ACAs in a broader category of patients.\(^{[16,37-39]}\) The most important point of evaluation is what the primary indication for prescription of anticoagulants was, and whether there is an on-going indication for anticoagulation.

Anticoagulants may be discontinued if they were prescribed for these indications:\(^{[16]}\)
- Paroxysmal Atrial fibrillation with CHA2DS2-VASc score of 1 or less.
- Acute MI without LV clot
- Recovered acute stress cardiomyopathy (Takotsubo cardiomyopathy)
- Bioprosthetic heart valve >3 months ago
- Post-surgical VTE prophylaxis
- First episode of provoked VTE >3 months ago

For on-going indications as in the high risk patients, the following factors must be accounted for:\(^{[16]}\)
- Whether ICH occurred due to poor dose titration of warfarin and supratherapeutic INR levels?
- Presence of concomitant anticoagulant and antiplatelet therapy
- Acute or worsening renal function, resulting in higher levels of NOAC or LMWH
- Drug interactions from other medication causing higher levels of anticoagulants
- “Herbal medications” such as fish oil, St. John’s wort etc.

A recent meta-analysis showed that significant diversity in clinical practise exists in ACA therapy after ICH. Anticoagulants were resumed only in 38.4% cases out of 2044 cases. This occurred between 10-39 days. Of those who did not resume anticoagulants, 17.6% suffered thromboembolic complications which was significantly worse than 6.7% in anticoagulated group. Importantly, no difference was observed in the rates of recurrent ICH in both those groups (8.7% vs 7.8%).\(^{[37]}\) The fact that a single episode of ICH is in itself a risk factor for recurrent ICH is a very important point that needs to be considered. This is more common for lobar haemorrhages that are frequently associated with cerebral amyloid angiopathy.\(^{[36,38-41]}\) The BRAIN study – Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding – showed that in-hospital re-initiation of warfarin therapy occurred in 32% cases and it did not contribute to any increase in 30-day death rates (aOR 0.49).

In general APAs, especially aspirin, are probably only modestly associated with an increased incidence of ICH, if at all.\(^{[42]}\) Studies have shown that antiplatelet use does not appear to dramatically increase the risk of haematoma expansion,\(^{[43,44]}\) nor is it associated with significant risk of recurrence of ICH. In fact, a strategy of early re-initiation of aspirin has been a popular ‘safe’ practice in patients who require anticoagulation but were not anticoagulated for the risk of haemorrhage. Although it does not provide equivalent protection against thrombotic complications, it is beneficial in terms of risk of recurrent haemorrhage.\(^{[15,38]}\)

### Timing of re-initiation of anticoagulants after ICH

As mentioned in the meta-analyses in the preceding section, this practice varies, with a range of 2.5 – 124 days.\(^{[38]}\) ACC guidelines suggest delaying the reinitiating of anticoagulants for about 1 month after ICH in patients without mechanical heart valves.\(^{[3]}\) A survey of 504 physicians showed that there was a preference for earlier re-initiation between 4-14 days in patients with mechanical heart valves.\(^{[45]}\) A recently published observational cohort study studied patients on chronic warfarin therapy for mechanical heart valves with or without AF. Re-initiation of therapeutic anticoagulation within 13 days of the ICH was associated with significantly increased hazard ratio for repeat
ICH (HR 7.06). A composite outcome analysis of haemorrhagic and thromboembolic complications suggested that the earliest safe time for re-initiation of therapeutic anticoagulation was 6 days, and this shortened cut-off point should be reserved for patients with very high thrombotic risks only. This specifically applied to a subset of patients with mechanical heart valves co-existing with atrial fibrillation, mitral valve prosthesis or cage-ball valve type.46

6. Venous thrombo-embolism prophylaxis in neurosurgical patients

The incidence of VTE in neurosurgical patients is estimated to be as high as 29-43% in patients who do not receive VTE prophylaxis, with PE occurring in 5% of the cases.47 A study from India showed an incidence rate of 12.08% for DVT in neurosurgical patients.48 Important risk factors that were identified were presence of hypertension (doubled the risk), obesity, alcoholism, smoking, malignant brain tumour, meningioma, prolonged surgery (longer than 5 hours), post-operative motor deficits, and delayed ambulation by more than 2 days after surgery. The results from the NSQIP database showed that cranial surgery has three times higher risk of VTE than spinal surgery (3.4% vs 1.1%).49 Brain tumour surgery gets complicated by VTE in 2-10% cases,50 and 3.5-18% of patients who present with aneurysmal subarachnoid haemorrhage develop VTE.51 Although spinal surgery in general has a lower propensity to trigger a DVT and enjoys the reputation of being in the low-to-moderate risk category in ACCP 2012 guidelines,52 spinal deformity correction surgeries, and spinal trauma surgeries share a fairly high rate of VTE events (2-19% and 0-14% respectively).53

The importance of VTE prophylaxis lies in the fact that a significant number (upto 25%) of DVTs may remain asymptomatic and may manifest directly as pulmonary embolism.54 Clinical examination is highly insensitive in diagnosing DVT. Studies have shown that nearly 50% of imaging proven DVT remains undiagnosed clinically, and about 46% patients with classic symptoms turn out to be imaging-negative.55

VTE prophylaxis

VTE prophylaxis should be considered in the following settings:
- During surgery under general anaesthesia, for all patients
- Any patient in altered sensorium, with a motor response of <M6
- Any patient with a limb paresis, power < MRC grade 4/5 (especially lower limb). Spinal cord injury patients should receive VTE prophylaxis as soon as treatment is instituted in a hospital setting.
- Immobilization or bed-bound status for any reason
- Patients with meningiomas, malignant gliomas and brain metastases, with motor deficits or altered sensorium. Ideally, these patients should receive pre-operative VTE prophylaxis with LMW heparin (except the meningioma group), since a patient with a malignant glioma and limb paresis is at high risk for VTE. However, VTE prophylaxis with LMW heparin in the pre-operative period is associated with a slightly increased of tumour bleed.58 If one opts to use LMW heparin in the pre-operative period, the last dose should be at least 12 hours prior to the start of surgery. Non-pharmacologic VTE prophylaxis is a viable option in these patients.

The modalities available for VTE prophylaxis are:
1. Mechanical thromboprophylaxis
   a. Antiembolism stockings/Graduated compression stockings
   b. Intermittent Pneumatic compression devices
   c. Foot impulse devices (Foot pumps).
2. Pharmacological thromboprophylaxis.

Pharmacological prophylaxis versus mechanical prophylaxis in neurosurgical patients

Both the NICE and the American Society of Hematology Draft recommendations suggest the preferential use of mechanical prophylaxis in neurosurgical patients unless there is a high risk of VTE and a compelling indication for pharmacotherapy.56,57 It is advised to use LMWH based on clinical judgement and in the high VTE risk group only. Pharmacological prophylaxis is contraindicated in presence of a ruptured, unsecured intracranial aneurysm or arteriovenous malformation or ICH, unless the condition has been stabilized.
Contrary to these guidelines, more evidence is accumulating in favour of the safety profile of anticoagulant use for VTE prophylaxis. Several studies have found no increased incidence of haemorrhagic complications with pharmacoprophylaxis.[58-60] The results of a prospective observational study in which LMWH was used for thromboprophylaxis starting one day postoperatively showed only 1% rate of ICH. This is not different from the reported incidence of post-operative hemorrhages in craniotomy patients without anticoagulant use, in the range of 1-1.5%. [60] A recent meta-analysis which included only prospective studies concluded that anticoagulant thromboprophylaxis is beneficial in VTE prevention, without any significant increase in either major or minor bleeding complications in neurosurgical patients. [60] The incidence of major intracranial haemorrhage in treatment group was 2.7% which was not statistically different from 1.6% in control group.

Despite abundant supporting data from meta-analyses and placebo-controlled randomized controlled trials across all disciplines of medicine, the reluctance of neurosurgeons to use pharmacological prophylaxis for VTE is probably based more on convention than conviction. Moreover, in pediatric neurosurgery, the safety of use of pharmacological thromboprophylaxis has not been documented and it is not recommended. Mechanical devices must be used, however, for VTE prophylaxis.[61,62]

A few pointers regarding VTE prophylaxis in neurosurgery

It should be borne in mind that most of the recommendations come from general medical literature and are not specific to neurosurgical population. The American Society of Hematology 2018 guidelines and NICE 2018 guidelines both recommend using LMWH preferably over UFH.[56,57] The recommendations for fondaparinux are less vehement, and it may be preferred over UFH and used as an alternative to LMWH, especially in cases where LMWH is contraindicated. In patients with Heparin-induced thrombocytopenia (HIT), fondaparinux is the preferred agent.

The recent American Society for Hematology (ASH) recommendations for medical patients (2018) have identified that the addition of mechanical devices to anticoagulants for VTE prophylaxis may cause more harm than good.[57] Although this is a conditional recommendation with low quality evidence, it is interesting to note that they mention of higher complications like falls, limb ulceration and ischemia which mechanical methods which tilt the equation against using combined methods. This is different from the ASH draft recommendations for surgical patients (2018) where they have clearly mentioned that combined methods are acceptable to use. The NICE guidelines suggest that for high VTE risk patients, a combined method of VTE prophylaxis is better.[56]

Timing of VTE Prophylaxis

Most authors recommend early initiation of mechanical VTE prophylaxis, starting at admission and no later than 24 hrs. Mechanical devices should be continued during the entire period of surgery, and beyond. There are aggressive VTE prophylaxis protocols which recommend starting UFH at 8 hrs post-operatively, and there are other protocols which recommend prophylaxis with LMWH after post-operative imaging on first post-operative day (usually 24 hrs after surgery). A slightly more disease/site – specific protocol that is followed by Agarwal et al.[63] from Pittsburgh as also shown to have excellent outcomes. They used subcutaneous UFH 5000 U every 8 hourly starting from first post-operative day after spine surgery, 2nd post-operative day after cranial surgery, and by 4th postoperative day for SDH, EDH and ICH.[63]

The status of inferior vena cava (IVC) filters

The primary indication to use IVC filters is to prevent the catastrophic complication of PE due to a DVT in cases where pharmacologic anticoagulation is contraindicated by other systemic factors. This also applies conditions where anticoagulation therapy has been complicated by haemorrhagic complications or has failed to prevent VTE. In a neurosurgical setting, full-dose therapeutic anticoagulation may be very risky in the early post-operative period (especially within the initial 4-5 days postoperatively), and in patients with ICH who have been managed non-surgically. Haemorrhagic stroke is also a contraindication for therapeutic anticoagulation. In such select cases, IVC filters may be used temporarily to prevent PE secondary to DVT. The FDA issued a statement in 2010 that these filters must be retrieved once their purpose is served. However, despite being an attractive option, the reputation of IVC filters has been poor. Most authorities
do not recommend use of IVC filters as primary prophylaxis, and that it must be used only in select cases where appropriate indication exists. Another problem is that IVC filters are inherently thrombogenic (although this is much less with newer generation products), and can be associated with multiple short-term and long-term complications. These include misplacement, hematoma, filter migration, air embolism, IVC perforation and thrombosis, hardware fracture and lower limb edema. Therefore, judicious use of IVC filter is suggested only in cases where therapeutic anticoagulation is contraindicated or failed or complicated, and not as a primary prophylactic means.

**Conclusion**

The intersection between anti-haemostatic medications, and neurosurgery is a complex one. We have summarized the best evidence available currently, but management of
these patients should be individualized. We have summarized our institutional protocol in Figure 2, and this may be employed as a template to manage these patients. VTE prophylaxis is an important issue in all bed bound patients and those with neurologic deficits and should be instituted in a timely fashion.

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References


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