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Thromboprophylaxis and Its Implications in Regional Anesthesia

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Abstract

Venous Thromboembolism (VTE) is an important cause of postoperative morbidity and mortality, especially when patients with co-morbid conditions (like obesity, coronary artery disease, or cancer) are on the rise. This necessitates the use of various thromboprophylaxis measures to prevent the occurrences of fatal VTE. However, the pharmacological thromboprophylaxis carries an inherent risk of bleeding, especially when the area of invasive work involves a potential space with risk of non-compressible arterial puncture. During neuraxial anesthesia, such bleeding into a closed space can result in spinal hematoma, which carries various neurological sequelae and requires urgent diagnosis and management.

We will be discussing the relevant literature pertaining to the modalities of thromboprophylaxis, their mechanism of action and optimal management of such patients in the perioperative setting.

Keywords: Thromboembolism; Thromboprophylaxis; Bleeding; Spinal hematoma; Anesthesia;

Introduction

Venous Thromboembolism (VTE), which encompasses Pulmonary Embolism (PE) and Deep Venous Thrombosis (DVT), is the major cause of morbidity and mortality in hospitalized patients [1,2]. VTE in hospitalized patients is asymptomatic. Furthermore, noninvasive tests, such as compression ultrasonography, have limited sensitivity for a diagnosis of asymptomatic DVT. Thromboprophylaxis, though mostly underused, is the most effective strategy to reduce morbidity and mortality from DVT [1]. Despite this evidence, thromboprophylaxis carries an inherent risk of bleeding especially when used in perioperative settings.

Bleeding is classified as major if it is intracranial, intraspinal, intraocular, mediastinal or retroperitoneal, leads directly to death, or results in hospitalization or transfusion [3]. Various data demonstrate that the presence of anticoagulants, at any time during Central Neuraxial Block (CNB) must be considered critical in the formation of spinal bleeding complication [4,5].

An extensive literature search was done using various sources like Pubmed, Indmed, Cochrane systemic reviews, Google Scholar, as well as the reading material and journals at our disposal. All the relevant literature in English language, published later than 1990 and indexed in reputable agency was selected.

Pathophysiology of Thrombosis

The pathogenesis is multifactorial in origin [2]. Venous thrombosis occurs when red blood cells, fibrin and, to a lesser extent, platelets, and leucocytes form a mass within an intact vein. Virchow's triad named after German pathologist Rudolf Virchow has been proposed to cause thrombosis and it includes: alteration in blood flow (stasis and turbulence), vascular endothelial injury, or alterations in the blood coagulability [2,6].

Incidence and Risk Factors

The exact prevalence of venous thrombosis is unknown. Clinical signs and symptoms are non-specific, only occurring in up to 50% of patients while sensitivity and specificity of screening test to detect disease in asymptomatic patients is low [6,7]. Annual incidence of Deep Venous Thrombosis (DVT) in general population is 0.5-1 per 1000. However this figure increases up to an estimated one in four hospitalized patients who possess one or more risk factors described below [7]. Venous Thromboembolism (VTE) remains a major source of morbidity and mortality in obstetrics with an incidence of 29.8/100,000 vaginal delivery hospitalizations; cesarean delivery confers a 4-fold increased risk of thromboembolism when compared with vaginal delivery [8]. Similarly the risk of VTE is increased several folds in patients with cancer [9,10]. The most serious and, potentially life threatening complication is a Pulmonary Embolus (PE) and occurs in about a third of those with an identified DVT. A similar number also suffer from chronic post-thrombotic leg syndrome typified by symptoms with leg pain, swelling, and skin ulceration [6].

Risk factors for venous thromboembolism includes major medical illnesses, obesity, previous VTE, cancer, age over 60 years [1,9]. Also included in this list is prolonged immobilization, lower limb paralysis (including anesthesia for more than 30 min), use of hormonal therapy (oral contraceptives, hormonal replacement therapy), chemotherapy (including tamoxifen) and co-morbid conditions, such as stroke, congestive heart failure or recent myocardial infarction, or varicose veins [2,6]. Biochemical abnormalities also may predispose to VTE. They can be inherited or acquired. Inherited abnormalities include deficiencies of antithtrombin, protein C or protein S, prothrombin gene mutation.

Acquired deficiencies include antiphospholipid antibody syndrome, myeloproliferative disorders, particularly essential thrombocythemia, and paroxysmal nocturnal hemoglobinuria [1,2,6]. Various models like Caprini score are being used to estimate VTE risks among the patients [11].

Clinical settings associated with high incidence of VTE include major orthopedic surgery of lower limbs, surgery for cancer, neurosurgery, acute spinal cord injury and multiple traumas [1].

Although thromboembolism remains a source of significant perioperative morbidity and mortality, its prevention and treatment are also associated with risk [3]. There is risk of bleeding associated with therapeutic anticoagulation and thrombolytic therapy. Risk factors for major bleeding during anticoagulation include intensity of anticoagulant effect, increased age, female sex, history of gastrointestitnal bleeding, concomitant aspirin use, and length of therapy. The incidence of hemorrhagic complications during therapeutic anticoagulation with intravenous or subcutaneous heparin is less than 3%; the risk associated with LMWH is slightly lower. Thrombolytic therapy represents the greatest risk of bleeding, with major hemorrhage occurring in 6% - 30% in patients treated for DVT, ischemic stroke, or ST elevated myocardial infarction [3].

Spinal hematoma after Central Neuraxial Block (CNB) is very rare, which makes the quantification of its probability very difficult [3]. The incidence is approximated to be less than 1 in 150,000 epidural and less than 1 in 222,000 spinal anesthetics. Finally, for medico-legal reasons, the real number of spinal hematomas subsequent to CNB may be higher than that reported in the literature [3,4]. Neurological compromise is presented as progression of sensory or motor block (68% of patients) or bladder/bowel dysfunction (8% of patients), and severe radicular back pain [2-4]. Although only 38% of the patients had partial to good neurologic recovery, spinal cord ischemia tended to be reversible in patients who underwent laminectomy within 8 hrs of onset of neurologic dysfunction [3]. However, surgical management versus conservative approach is debatable [12]. Prompt diagnosis and treatment is essential [4]. Moreover, a bloody/difficult tap will complicate an anticipated uncomplicated anesthetic course in anticoagulated patients. Insertion of epidural catheter appeared to be just as critical, because bleeding occurred at that moment in almost half of the cases in a study [4]. Spontaneous epidural spinal hematoma is a rare condition, with an uncertain etiology. In half of the cases, no predisposing factor is identified despite extensive evaluation [12].

Management

Venous Thromboembolism (VTE) is a common cause of preventable death in hospitalized patients. Approximately one-third of the 150,000-200,000 VTE-related deaths occur following surgery. The high incidence of VTE and the availability of effective methods of prevention mandate that thromboprophylaxis should be considered in every surgical patient [13].

Venous thromboembolism (VTE) is often due to prophylaxis failure rather than omission. Risk factors for thromboprophylaxis failure include personal or family history of VTE, use of vasopressors or inotropes, increased body mass index, cranial surgery, intensive care patient, leukocytosis, indwelling central venous catheter and admission from a long-term care facility [14,15].

Those with low risks of VTE do not need specific therapy apart from early mobilization, whereas those with moderate to high risk should receive thromboprophylaxis [1]. Thromboprophylaxis measures include pharmacologic and non-pharmacologic agents. Mechanical methods serve to prevent venous stagnation in the lower limbs by promoting venous outflow, whereas pharmacologic methods act by attenuating coagulation [1,9,13]. Mechanical methods include Intermittent Pneumatic Compression (IPC), anti-embolic stockings or Elastic Stockings (ES), foot impulse devices, and physiotherapy and nursing. Mechanical prophylaxis alone, are inadequate to prevent PE and thromboprphylaxis by anticoagulants is essential [2]. Pharmacological agents include anticoagulants such as Unfractionated Heparin (UFH), Low-Molecular Weight Heparin (LMWH), and warfarin, or antiplatelet agents, particularly acetylsalicylic acid and thienopyridines. A recent addition is synthetic pentasaccharide, fondaparinux, (for high-risk orthopedic patients) and thrombin and activated factor Xa inhibitors [1,2,3,6]. Though newly added coagulation-altering therapies creates additional confusion to understanding commonly used medications affecting coagulation in conjunction with Regional Anesthesia (RA), there is promising new evidence that Novel Oral Anticoagulants (NOACs) are more effective in thromboprophylaxis and preventing DVT. In addition, fixed dose administration, reduced need for monitoring, fewer requirements of dose adjustment, and more favorable pharmacokinetics and pharmacodynamics are likely to streamline perioperative management, simplify transitioning of agents, diversify "bridging therapy" options and reduce risk costs.[16]

Thromboprophylaxis in Various Clinical Settings: [1]

General Surgery: Low dose UFH (5000U subcutaneously 2-3 times daily starting 2 h before the procedure) and LMWH are effective. Initiation of therapy preoperatively may prevent DVT during or immediately after surgery. In high risk patients, IPC or elastic stockings are combined with low-dose UFH or LMWH. Acetylsalicyclic acid is not recommended as the sole form of thromboprophylaxis in general surgery patients. Warfarin given postoperatively can be an alternative to parenteral anticoagulants.

General surgery in cancer patients: patients who undergo general surgery for cancer have 29% incidence of venographically-detected DVT compared with 19% in those without cancer. Use elastic stockings in conjunction with either UFH or LMWH are given.

Major orthopedic surgery: patients have increased incidence of postoperative VTE. Consequently primary prophylaxis is mandatory and that too for extended period for at-least 10days. Patients with risk factor for VTE or those who are not mobile should receive prophylaxis with LMWH or warfarin for 30 days.

Elective hip arthroplasty: without prophylaxis, incidence

of venographically-detected DVT is 51%. LMWH or warfarin is shown to be effective. Preoperative low dose UFH followed by postoperative UFH in doses adjusted to maintain activated Partial Thromboplastin Time (aPTT) at, or just above the upper range of normal (so-called adjusted-dose UFH) is also effective and safe. But frequent monitoring is necessary. Neither elastic stockings nor pneumatic compression reduces the incidence of proximal DVT in hip arthroplasty, although both lower the incidence of calf DVT. Fondaparinux is also effective, but cost considerations limit it.

Elective knee arthroplasty: without prophylaxis, incidence of venographically-detected DVT is 61%. LMWH and warfarin are less effective for preventing DVT following knee arthroplasty than hip replacement. This reflects their inability to reduce the rate of distal DVT in knee surgeries. Intermittent pneumatic compression is a reasonable alternative to LMWH or warfarin in patients at high risk of bleeding.

Vascular or cardiac surgery: In low-risk patients, no specific prophylaxis is required except early ambulation. Patients with prolonged hospitalization, low-dose UFH or LMWH is given. IPC with or without ES is used in place of anticoagulants in those with risk of bleeding. Acetylsalicylic acid should be given for at-least one year to patients who undergo coronary artery bypass grafting and patients who have peripheral vascular reconstructive surgery. Clopidogrel or ticlopidine is alternative in acetylsalicylic acid intolerance.

Neurosurgery: IPC, with or without ES is recommended form of thromboprophylaxis. Postoperative low-dose UFH or LMWH is an alternative.

Based on low quality of data, the most recent recommendations by American College of Chest Physicians evidence based practice guidelines does not differentiate between twice daily dosing and TID dosing, defining them both as 'low-dose UFH'. Again, due to paucity of data regarding TID dosing, the American Society of Regional Anesthesia (ASRA), by consensus opinion, recommends 'the safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice-daily dosing of UFH has not been established. In author's institution, practitioners confirm a normal aPTT before removing the catheter in those receiving TID subcutaneous UFH. For those receiving BID, routine aPTT testing is not indicated. Because of heparin induced thrombocytopenia, it is recommended by guidelines that patient receiving heparin for more than 4 days have a platelet count assessed before neuraxial block and catheter removal. The study found that the routine use of aPTT testing on patients receiving TID subcutaneous UFH at the time of removal of epidural catheters as a risk-reduction strategy is not supported by their results. Given the rare incidence of neuraxial hematoma, definitive conclusions on the risks of TID subcutaneous UFH administration in patients receiving epidural analgesia cannot be drawn [17].

Guidelines

To manage patients on anticoagulation, basic pharmacokinetic rules to observe include the following: [16]

1) not performing neuraxial/deep-peripheral nerve blocks (PNBs) or catheter removal until at least 2-T1/2 (T1/2 depending on renal and hepatic function) after last anticoagulant administration for optimal risk/benefit ratio (25% pharmacodynamic efficacy or being more conservative with 5 - $T_{1/2}$ (3.125% anticoagulant in circulation) in high-risk patients or from new anticoagulant with limited clinical experience); 2) following catheter removal/neuraxial and deep needle puncture, next anticoagulant administration should be based on the time required to reach maximum activity, and 3) clinical vigilance during initial hrs/days.

American Society of Regional Anesthesia Guidelines

Perioperative Management of Antithrombotic and Antiplatelet Therapy

Minor procedures may not require their interruption. It is critical to determine whether the planned procedure necessitates interruption of antithrombotic/ antiplatelet therapy. In patients at moderate to high risk of thromboembolism, bridging therapy is recommended, when antithrombotic/ antiplatelet therapy is interrupted.

Fbrinilytic and Thrombolytic Therapy:

Anesthetic management of patients receiving thrombolytic therapy

1. In patients scheduled to receive thrombolytic therapy, it is recommended to avoid these drugs for 10 days after puncture of non-compressible vessel or surgery.

2. In patients who have received fibrinolytic and thrombolytic therapy, guidelines recommend against performance of spinal or epidural anesthetics except in highly unusual circumstances.

3. Guidelines suggest the measurement of fibrinogen levels (one of the last clotting factors to recover) to evaluate the presence of residual thrombolytic effect and appropriate timing of catheter removal.

Unfractionated Intravenous and Subcutaneous Heparin

Pharmacology of UFH: It inactivates thrombin (factor IIa), factor Xa and factor IXa. Large molecular weight heparin catalyzes inhibition of both factor IIa and Xa. Smaller ones only factor IIa. Intravenous injection results in immediate anticoagulant activity, whereas subcutaneous injection results in a 1 to 2 hrs delay. When given in therapeutic dose, anticoagulant effect is monitored with aPTT, especially during cardiopulmonary bypass.

One of the advantages of heparin anticoagulation is that its effect is rapidly reversed with protamine (1mg neutralizes 100U of heparin).

Intravenous UFH: it involves administration of 5,000 – 10,000U of heparin during the operative period, particularly in the setting of vascular surgery.

Recommendation- Heparin should be discontinued for 2 to 4 hrs before neuraxial catheter removal, coagulation status assessed before manipulation of catheter, and careful assessment of the presence of sensory and motor function in the lower extremities for at least 12 hrs after the catheter removal.

Subcutaneous heparin: 5000U of heparin subcutaneously every 12 hrs has been used extensively for prophylaxis of DVT. aPTT rarely exceeds 1.5 times the normal. Previous authors have recommended delaying performance of neuraxial blocks for two hours after the administration of subcutaneous heparin. However, this may actually coincide with the peak effect.

Anesthetic management of patients receiving UFH

1. With dosing regimens of 5000 U twice daily, there is no contraindication to the neuraxial techniques. The risk of neuraxial bleeding may be reduced by delay of the heparin injection until after the block and may be increased in debilitated patients after prolonged therapy.

2. The safety of neuraxial block in patients receiving doses greater than 10,000 U of UFH daily or more than twice-daily dosing of UFH had not been established. Risk-benefit analysis should be done.

3. Patients receiving more than 4 days have a platelet count assessed before neuraxial block and catheter removal. (Heparin-induced thrombocytopenia)

4. Remove the indwelling catheter 2 to 4 hrs after the last heparin dose and assess the patient's coagulation status; re-heparin 1 hr after catheter removal.

Low Molecular Weight Heparin

The elimination half-life is 3-6 hrs after subcutaneous injection and is dose dependent. AntiXa levels peak 3-5 hrs after administration. Because half-life is 3-4 hrs times that of UFH, a significant anticoagulant activity is still present 12 hrs after injection. Half- life also increased in patients with renal failure. LMWHs vary both biochemically and pharmacologically. LMWH has been demonstrated to be efficacious as a 'bridge therapy'.

The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher. Needle placement should occur at a minimum of 24 hrs after this level of LMWH anticoagulation.

Anesthetic management of the patients receiving LMWH

1. Anti-Xa level is not predictive of risk of bleeding, hence routine monitoring not recommended.

2. Preoperative LMWH:

a) Needle placement 10-12 hrs after the LMWH. If patient is receiving higher doses, delay of at-least 12 hours is recommended at the time of needle placement.

b) In patients administered LMWH 2 hrs preoperatively, guidelines recommend against neuraxial technique because needle placement would occur during the peak anticoagulant activity.

3. Postoperative LMWH:

a) Twice-daily dosing. Associated with increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24hrs postoperatively. Indwelling catheter should be removed before the initiation of LMWH thromboprophylaxis. Administration of LMWH should be delayed 2 hrs after catheter removal.

b) Single-daily dosing: the first postoperative LMWH dose should be administered 6 to 8 hrs postoperatively. The second postoperative dose should occur no sooner than 24 hrs after the first dose. Indwelling neuraxial catheter may be safely maintained. Catheter should be removed 10-12 hrs after the last dose of LMWH. Subsequent LMWH dosing should occur at a minimum of 2 hrs after catheter removal.

Oral Anticoagulants (Warfarin)

Interfere with synthesis of vitamin K dependant factors (II(thrombin), VII, IX X).

Regional anesthetic management of patient on oral anticoagulants

1. Guidelines recommend that anticoagulant therapy must be stopped (ideally 4-5 days before the planned procedure) and the INR must be normalized before initiation of neuraxial block.

2. In patients receiving an initial dose of warfarin, INR should be checked before neuraxial block if first dose was given more than 24 hrs earlier or if the second dose of oral anticoagulant has been administered.

3. Patients receiving low-dose warfarin during epidural analgesia, INR to be checked daily.

4. As warfarin is initiated, neuraxial catheter should be removed when INR is less than 1.5.

5. INR greater than 1.5 and less than 3. *Cautious* removal of indwelling catheter.

6. In patients INR greater than 3, warfarin dose to be held or reduced in patients with indwelling neuraxial catheters. No definite recommendation could be made regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic level of anticoagulation.

Antiplatelet Medication

Includes NSAIDS, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban). Though Ivy bleeding time has been suggested as the most reliable predictor in patients receiving antiplatelet drugs, there is no evidence that a bleeding time can predict hemostatic compromise.

Thienopyridines (ticlopidine, clopidogrel) act by inhibiting adenosine diphosphate induced platelet aggregation and affect both primary and secondary platelet aggregation. Steady state is achieved within 7 days for clopidogrel and 14 to 21 days for ticlopidine.

Platelet GP IIb/IIIa receptor antagonists (abciximab, eptifibatida (intergrilin) and tirofiban) inhibit platelet aggregation.

Anesthetic management of patients receiving antiplatelet medication

1. Nonsteroidal anti-inflammatory drug represent no added significant risk for development of spinal hematoma.

2. The suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. If neuraxial blockade is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented.

3. Platelet GP IIb/IIIa inhibitors: After administration, the time for normal platelet aggregation is 24 to 48 hrs for abciximab and 4 to 8 hrs for eptifibatide and tirofiban. Neuraxial technique should be avoided until platelet function has recovered. Although they are contraindicated within 4 weeks of surgery, should one be administered in the postoperative period, neurological monitoring is recommended.

THROMBIN INHIBITORS (desirudin, lepirudin, bivalirudin, argatroban): inhibit both free and clot-bound thrombin.

Anesthetic management: guidelines recommend against the performance of neuraxial techniques

Fondaparinux: Causes factor Xa inhibition. Plasma half-life is 21 hrs, allowing single daily dosing, with first dose administered 6 hrs postoperative.

Anesthetic management: Catheters to be removed 36 hrs after the last dose, and subsequent dosing to be delayed for 12 hrs after catheter removal.

Oral Direct Thrombin and Activated Factor Xa Inhibitores in Development (dabigatran and rivaroxaban respectively): table 1.

Table 1: Recommended time intervals before and after neuraxial block or catheter removal

DRAFT		
DRUG	TIME before	TIME after
Dabigatran	5 days	6 hrs
Apixaban	3 days	6 hrs
Rivaroxaban	3 days	6 hrs
Prasugrel	7 -10 days	6 hrs
Ticagrelor	5-7 days	6 hrs.

Conclusion

It is an undeniable fact that any incidence of pulmonary embolism following deep venous thrombosis remains one of the commonest preventable causes of death in post-operative patients [2]. In perioperative setting, managing a patient on thromboprophylaxis therapy is still challenging, and with the introduction of various newer anticoagulants, management becomes the more perplexing. In-view of limited randomized trials pertaining to the thromboprophylaxis management in regional anesthesia setting, a thorough knowledge of the mechanism and duration of action of these anticoagulant drugs, as well as recommended guidelines is essential for the effective management of such patients.

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