CHAPTER 4: REGIONAL ANESTHESIA AND ANTICOAGULATION

Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy

The American Society of Regional Anesthesia (ASRA) convened its Third Consensus Conference on Regional Anesthesia and Anticoagulation and the revised guidelines were published in the January-February 2010 issue of the ASRA Journal. This chapter is mainly based on these guidelines.

Epidural hematoma is defined as a rare, but potentially catastrophic complication of spinal or epidural anesthesia. The introduction of low molecular weight heparin (LMWH) in the United States coincided with an increased number of reported cases of epidural hematoma. Although, it can happen spontaneously, its incidence increases with age, associated abnormalities of the spinal cord or vertebral column, underlying coagulopathy, difficult needle placement and an indwelling catheter in the presence of anticoagulation. The actual incidence of hemorrhagic complications in association with neuraxial anesthesia is unknown, but has been estimated at less than 1 in 150,000 for epidural and less than 1 in 220,000 for spinal anesthesia. Recent studies suggest that this incidence may be higher, some say as high as 1 in 3,000 in selected populations.

At the moment there is no laboratory model to study this problem and its rarity precludes a prospective randomized study. As a result the ASRA consensus represents the opinions of experts based on case reports, clinical series, pharmacology, hematology and risks factors for surgical bleeding.

Strength and grade of recommendations

A cornerstone in evidence-based medicine is the quality of the available evidence. The validity of the recommendation improves with the quality of the evidence. The quality of the available data is classified according to its quality into three levels:

- A: Highest level of evidence. These are randomized clinical trials and meta-analysis. Because neuraxial bleeding is rare this type of evidence is mostly not available.
- B: Inconsistent or limited quality patient-oriented evidence. These are observational and epidemiological series.
- C: recommendations derived from case reports or expert opinion.

The recommendations that are made based on the review of the data have also different levels depending on the strength of the guideline and the degree of consensus:

- Grade 1: represents general agreement on the efficacy of a treatment/procedure.
- Grade 2: Denotes conflicting evidence or opinion. 2a evidence is mostly in favor. 2b, Efficacy is less established.

- Grade 3: Suggests that the procedure m ay not be useful and possibly harmful (e.g., epidural procedure in a patient receiving twice-daily LMWH).

Risk factors for venous thromboembolism VTE

This is an important health care problem. Neuraxial anesthesia has been associated with improved patient outcomes, including mortality and major morbidity. This probably results from the "attenuation of the hypercoagulable response" and decreased venous thrombosis after these techniques. However the beneficial effect of neuraxial technique s on coagulation is insufficient as the sole m ethod of throm boprophylaxis. As a result, anticoagulants, antiplatelets and thrombolytic medications are commonly used in the pr evention and treatm ent of thromboembolism.

Nearly all hospitalized patients have at least one risk factor and 40% of patients have 3 or more risk factors (Geerts et al , as cited by the 2010 ASRA statement). The following is a table for risk factors for VTE taken from the 2010 ASRA statement:

TABLE 1. Risk Factors for VTE

Surgery
Trauma (major trauma or lower extremity injury)
Immobility, lower extremity paresis
Cancer (active or occult)
Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Central venous catheterization
Inherited or acquired thrombophilia

From Geerts et al,[7] with permission.

Accordingly, most hospitalized patients be nefit from some type of thromboprophylaxis. The following table, also taken from the AS RA 2010 statem ent, lists the recomm ended prophylaxis according to risk:

TABLE 2. Levels of Thromboembolism Risk and Recommended Thromboprophylaxis in Hospital Patients (Section 1.3)

Levels of Risk	Approximate DVT Risk Without Thromboprophylaxis, %*	Suggested Thromboprophylaxis Options
Low risk	<10	
Minor surgery in mobile patients		No specific thromboprophylaxis
Medical patients who are fully mobile		Early and "aggressive" ambulation
Moderate risk	10–40	
Most general, open gynecologic or urologic surgery patients		LMWH (at recommended doses), LDUH 2 times/d or 3 times/d, fondaparinux
Medical patients, bed rest or sick		
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§
High risk	40–80	
Hip or knee arthroplasty, hip fracture surgery		LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2–3)
Major trauma, spinal cord injury		
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis†

From Geerts et al,[7] with permission.

*Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.

†Mechanical thromboprophylaxis includes IPC, venous foot pump and/or graduated compression stocking: consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.

LDUH indicates low-dose UFH.

Because of concerns with surgical bleeding associated with thromboprophylax is, the American Academy of Orthopaedic Surgeons (AAOS) published its own guidelines in 2007 for the prevention of symptomatic PE in patients undergoing total joint replacement. The following table taken from the 2010 ASRA guidelines shows the AAOS recommendations:

TABLE 3. Chemoprophylaxis of Patients Undergoing Hip or Knee Replacement*

Patients at standard risk of both PE and major bleeding
- Aspirin, 325 mg 2×/d (reduce to 81 mg 1×/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 wk.
- LMWH, dose per package insert, starting 12–4 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d.
- Synthetic pentasaccharides, dose per package insert, starting 12–24 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d.
- Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk.

Patients at elevated (above standard) risk of PE and at standard risk of major bleeding
- LMWH, dose per package insert, starting 12–24 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d.
- Synthetic pentasaccharides, dose per package insert, starting 12–24 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d.
- Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk.

Patients at standard risk of PE and at elevated (above standard) risk of major bleeding
- Aspirin, 325 mg 2×/d (reduce to 81 mg 1×/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 wk.
- Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk.
- No chemoprophylaxis

Patients at elevated (above standard) risk of both PE and major bleeding
- Aspirin, 325 mg 2×/d (reduce to 81 mg 1×/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 wk.
- Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk.
- No chemoprophylaxis

From the AAOS Clinical Guideline on Prevention of Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty. Adapted May 2007.[23]

*All patients should be considered for intraoperative and postoperative mechanical prophylaxis in addition to appropriate chemoprophylaxis.

Administration of thromboprophylaxis

In terms of agents and doses, the 2010 ASRA statem ent recommends to follow the American College of Chest Physicians ACCP gui delines advising the clin icians to follow the manufacturer-suggested dosing guidelines (Evidence Grade 1C).

Risk of bleeding

Bleeding, especially intracranial, intraspinal, intraocular, mediastinal or retroperitoneal, is the most feared complication of anticoagulant and thrombolytic therapy. Risks fa ctors include

increased age, female sex, history of gastrointestinal bleeding, concomitant aspirin use and length of therapy.

During warfarin therapy an INR of 2.0 to 3.0 is associated with a 3% low risk of bleeding during a 3-month treatment period. Stronger regimens (INR >4) increase the risk of bleeding significantly to 7%.

The incidence of hemorrhagic complications during therapeutic anticoagulation with IV or subcutaneous heparin is less than 3% and even lower with LMWH.

Thrombolytic therapy is associated with the highest risk of bleeding, with major bleeding occurring in 6% to 30% of patients treated with thrombolytic therapy for DVT, ischemic stroke, or ST elevation myocardial infarction. There is no significant difference in the risk of bleeding among thrombolytic agents.

The addition of potent anticoagulants (LMWH, hirudin) or antiplatelets (glycoprotein IIb/IIIa agents) therapy increases even more the risk of major bleeding.

"Therefore, although thromboembolism remains a source of significant perioperative morbidity and mortality, its prevention and treatment are also associated with risk" (2010 ASRA statement, page 67).

Anesthetic management of the patient receiving thrombolytic therapy

These patients are at risk of serious bleeding. We will discuss several situations:

1. Patients scheduled to receive thrombolytic therapy: Avoid performing lumbar punctures and neuraxial anesthesia and avoid thrombolytic therapy for 10 days if these procedures have been performed (evidence Grade 1A).
2. Patients who have received thrombolytic therapy: Do not perform spinal or epidural procedures (Evidence Grade 1A). Data not available as to how long we need to wait.
3. Patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy: Neurological monitoring every 2 hours or less "for an appropriate interval". If epidural catheter present avoid drugs producing sensory and motor block to facilitate neurological assessment (Evidence Grade 1C).
4. Patient with an epidural catheter who unexpectedly received thrombolytic therapy: There is no definite recommendation as to when to remove it. They suggest to measure fibrinogen levels (one of the last clotting factors to recover) for appropriate timing of catheter removal (Evidence Grade 2C).

Anesthetic management of the patient receiving unfractionated heparin (UFH)

There is a long experience in the management of these patients. However recent guidelines suggesting a three-time dose (thrice daily) of subcutaneous heparin for some patients and its potential for increased bleeding have prompted a modification to the ASRA guidelines as follows:

1. Daily review of patient's medical records to identify the concomitant use of other drugs affecting coagulation like antiplatelets, LMWH and oral anticoagulants (Grade 1B).
2. Patients receiving 5000 U of UFH twice daily do not have contraindication for neuraxial techniques. The risk of bleeding may be reduced by delay of the heparin dose until after the block. The risk may be increased in debilitated patients after prolonged therapy (Grade 1C).

3. The safety of neuraxial blocks on patients receiving more than twice daily dose o r doses greater than 10000 U of UFH daily has not been established. Suggest frequent neurological exam if neuraxial has been done (Grade 2C).
4. Patients receiving heparin for m ore than 4 days (heparin-induced throm bocytopenia) should have a platelet count before neuraxial block and catheter removal.
5. Combining neuraxial techniques with intr aoperative anticoagulation with heparin during vascular surgery is accep table with the following recommendations (Grade 1A):

    a. Avoid the technique in patients with other coagulopathies.
    b. Delay heparin administration for 1 hr after needle placement.
    c. Remove catheter 2-4 hr after the last heparin dose; re-heparin 1 hr after catheter removal.
    d. Monitor the patient postoperatively to provide early detection of motor blockade. Avoid local anesthetics through catheter.
    e. The occurrence of bloody or difficult ne uraxial technique m ay increase risk, but data does not support m andatory cancellation. Risk-benefit discussion with surgeon about proceeding.
    f. Insufficient data exist about risk of bleeding when neuraxial techniques are combined with the full an ticoagulation of cardiac surgery. They su ggest neurological monitoring and avoidance of local anesthetics (Grade 2C).

Anesthetic management of the patient receiving LMWH

The extensive European experience is us eful to us. The 2010 ASRA consensus respects the labeled dosing regim ens of LM WH as es tablished by the Food and Drug Adm inistration. Although it is impossible to eliminate the risk of neuraxial hematoma previous recommendations have been deemed useful.

1. The anti-Xa level is no t predictive of the risk of bleeding. Recommend agains t the routine use of it (Grade 1A).
2. Antiplatelets and oth er anticoagulants administered in conjunction with LMWH increase the risk of spinal hem atoma. Avoid concomitant use of antiplatelets drugs, unfractionated heparin, or dextran regardless of LMWH dosing regimen (Grade 1A).
3. The presence of blood during neuraxial te chnique does not necessitate postponem ent of surgery. Recommendation to delay initia tion of LM WH for 24 hr in discussion with the surgeon (Grade 2C).

4. <u>Preoperative use of LMWH</u>:
    a. Patients receiving LMWH can be assu med to have altered coagulation. Recommend needle placement at least 12 hr after the LMWH last dose (Grade 1C).
    b. Patients receiving higher doses of LM WH, such as enoxaparin 1 m g/kg every 12 hrs, enoxaparin 1.5 m g/kg daily, dalteparin 120 U/kg every 12 hrs, dalteparin 200 U/kg daily, or tinzapar in 175 U/kg daily, the recomm endation is to delay neuraxial technique for at least 24 hrs (Grade 1C).

c. Patients given a dose of LMWH 2 hrs preoperatively (general surgery patients) the recommendation is to avoid neuraxial techniques because of peak anticoagulant activity (Grade 1A).

5. Postoperative use of LMWH: Patients to undergo post operative LMWH prophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule (Grade 1C):
   a. Twice-daily dosing. This dosing is associated with increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hrs postoperatively. Indwelling catheters may be left in place overnight but must be removed before initiation of LMWH, and the first dose should be delayed for 2 hrs after catheter removal.
   b. Single-daily dosing. The first postoperative LMWH dose should be administered 6-8 hrs postoperatively and the second no sooner than 24 hrs later. Indwelling catheters may be safely maintained although it should be removed a minimum of 10-12 hrs after the last dose of LMWH. Subsequent dosing should not be given for at least 2 hrs after catheter removal. No other drugs with effect in coagulation should be given because of risk of additive effects.

Regional anesthetic management of the patient on oral anticoagulants

The management of patients receiving perioperative warfarin remains controversial.

1. In the first 1-3 days after warfarin discontinuation the coagulation status (reflected primarily by factors II and X levels) may not be adequate despite a decrease in the INR (indicating a return of factor VII activity). Adequate levels of II, VII, IX and X may not be present until the INR is normal. The recommendation is that warfarin must be stopped 4-5 days prior to the procedure and the INR measured before a neuraxial block is attempted (Grade 1B).
2. Avoid using other drugs with anticoagulation effect like aspirin and other NSAIDs, ticlopidine, and clopidogrel, UFH, and LMWH (Grade 1A).
3. In patients who are likely to have an enhanced response to the drug, it is recommended to use the available algorithms to guide in the dosing based on desired indication, patient factors, and surgical factors (Grade 1B).
4. In patients receiving an initial dose of warfarin before surgery, the recommendation is to check the INR prior to neuraxial block if the first dose of warfarin was administered more than 24 hrs earlier or if a second dose has been administered (Grade 2C).
5. In patients receiving low-dose warfarin therapy during epidural analgesia, the suggestion is to monitor the INR daily (Grade 2C).
6. For patients on warfarin therapy receiving epidural analgesia neurologic testing of motor and sensory function should be performed routinely. To facilitate the neurologic evaluation keep the local anesthetics to a minimum (Grade 1C).
7. As warfarin therapy is initiated it is suggested that neuraxial catheters should be removed with an INR of less than 1.5. This value correlates hemostasis with clotting

factor activity levels greater than 40%. The suggestion is to keep neurologic testing after catheter removal for at least 24 hrs (Grade 2C).

8. In patients with INR more than 1.5 but less than 3 the suggestion is to remove catheters with caution after reviewing medication records for other medications affecting coagulation that may not affect the INR (e.g., NSAIDs, clopidogrel, ticlopidine, UFH, LMWH (Grade 2C). It is also recommended to check neurological status before catheter removal and continued until the INR has stabilized at the desired prophylaxis level (Grade 1C).
9. In patients with INR greater than 3 and an indwelling catheter, the recommendation to hold or reduce the warfarin dose (Grade 1A). No definitive recommendation can be made for removal of catheters in patients with therapeutic levels of anticoagulation (Grade 2C).

Anesthetic management of the patient receiving antiplatelets medications

Antiplatelet medications exert diverse effects on platelet function. These drugs include NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel) and platelet glycoprotein (GP) IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban). There is no wholly accepted test, including the bleeding time, to guide antiplatelet therapy.

1. NSAIDs seem to present no added significant risk of spinal bleeding related to neuraxial techniques. No specific concerns exist at this time about this drugs and the timing of single-shot or catheter insertion or removal (Grade 1A).
2. In patients receiving NSAIDs, the recommendation is not to perform neuraxial techniques if other drugs like oral anticoagulants, UFH, and LMWH are being used concurrently. Cyclooxygenase-2 (cox-2) inhibitors have minimal effect on platelet function and should be considered in patients requiring anti-inflammatory therapy in the presence of anticoagulation (Grade 2C).
3. The actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown. Recommendations are based on labeling precautions and the clinical experience (Grade 1C).

    a. On the basis of labeling and surgical experience the waiting period between discontinuation of a drug and neuraxial block is:
        i. ticlopidine: 14 days
        ii. clopidogrel: 7 days. If a neuraxial block is indicated between 5-7 days after its discontinuation, normalization of platelet function should be documented.

    b. Platelet GP IIb/IIIa inhibitors have a profound effect on platelet aggregation. Neuraxial techniques should be avoided until platelet function has recovered. This time is:
        i. Abciximab: 24-48 hrs
        ii. Eptifibatide and tirofiban: 4-8 hrs.

Anesthetic management of the patient receiving herbal therapy

Herbal drugs by themselves do not interfere with the performance of neuraxial techniques. The recommendation is against mandatory discontinuation of herbs or avoidance of regional techniques in these patients (Grade 1C).

Anesthetic management of patients receiving thrombin inhibitors (desirudin, lepirudin, bivalirudin, and argatroban)

In these patients the recommendation is not to perform neuraxial techniques (Grade 2C).

Anesthetic management of the patient receiving fondaparinux

The actual risk is unknown. Until further experience is available, performance of neuraxial techniques should be avoided.

Anesthetic management of the anticoagulated parturient

In the absence of large series of neuraxial technique in pregnant women receiving anticoagulation the recommendation is to follow the ASRA guidelines for the rest of surgical patients (Grade 2C).

Anesthetic management of the patient undergoing plexus or peripheral block

The recommendation is to apply the ASRA guidelines for neuraxial techniques (Grade 1C).

References

1. Neal JM: Neural Blockade and Anticoagulation. In: Regional Anesthesia, The Requisites in Anesthesiology. Rathmell J, Neal J, Viscomi C (eds). Philadelphia, Elsevier Mosby, 2004, pp 151-156
2. Bergqvist D, Wu CL, Neal JM. Anticoagulation and Neuraxial Regional Anesthesia: Perspectives. [Editorial] Reg Anesth Pain Med 2003; 28: 163-166
3. Horlocker tt, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: Defining the risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003; 28: 172-197
4. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy. American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010; 35: 64-101