

AANA JOURNAL COURSE

Update for nurse anesthetists

2

*6 CE Credits

Anticoagulation and spinal and epidural anesthesia

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An increasing number of surgical patients preoperatively are taking anticoagulant medications. These patients are at an increased risk for development of epidural hematoma with spinal or epidural anesthesia. It is the responsibility of the anesthesia provider to understand and anticipate this risk and to alter the anesthetic plan accordingly.

The purpose of this AANA Journal course is to update anesthesia providers regarding the common anticoagulants used for surgical patients, the risks associated with epidural and spinal anesthesia in conjunction with anticoagulation, and recommendations for the use of epidural and spinal anesthesia

in anticoagulated patients. Antiplatelet drugs, oral anticoagulants, heparin, low-molecular-weight heparin, other new anticoagulants, and herbal medications are reviewed.

When spinal or epidural anesthesia is considered for a patient who has been taking anticoagulant medications, the risk of epidural hematoma vs the benefits of regional anesthesia must be weighed carefully. Appropriate management of the patient extends well into the postoperative period and should include anesthesia providers, attending physicians, and nurses.

Key words: Anticoagulation, epidural anesthesia, epidural hematoma, spinal anesthesia.

Objectives

At the completion of the course, the reader should be able to:

1. Explain the pathophysiology related to spinal and epidural hematomas.
2. Review the incidence, risk factors, and diagnostic testing for an epidural hematoma in patients taking anticoagulants.
3. Discuss an evidenced-based review of complications and side effects of the concurrent anticoagulants related to spinal and epidural anesthesia.
4. Describe the pharmacological mechanism of action of commonly encountered anticoagulant drugs.
5. Discuss current recommendations for anticoagulants and spinal and epidural anesthesia.

Introduction

Regional anesthesia has been shown to offer beneficial outcomes over general anesthesia. These benefits include lower incidence of postoperative nausea and vomiting, improved postoperative pain relief, earlier ambulation, and a decrease in surgical blood loss. Furthermore, in the debilitated patient, regional anesthesia offers the benefit of less alteration in the patient's baseline cardiac and pulmonary status. Although these benefits of spinal and epidural anesthesia have been demonstrated, a significant degree of debate exists over their use with patients taking anticoagulants. This concern stems from an apparent relationship among the triad of epidural hematoma, anticoagulation, and regional anesthesia. Many patients receiving anticoagulants have undergone epidural or

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spinal anesthesia and have not developed hematomas. Conversely, patients not receiving anticoagulants have developed spontaneous epidural hematomas.

Anesthesia professionals have been unable to reach a consensus about the proper use of epidural and spinal anesthetics with patients receiving anticoagulants. The concern is related to the increasing use of new anticoagulants, each with specific indications for use in thrombotic prophylaxis. It is the responsibility of the anesthesiologist who administers regional anesthesia to understand the risk for epidural hematoma with concurrent anticoagulation. The American Society of Regional Anesthesia and Pain Medicine (ASRA) has recommended guidelines for the use of regional anesthesia in patients taking anticoagulants. The purpose of this article is to provide a review for anesthesia providers regarding the risks associated with epidural and spinal anesthesia in conjunction with anticoagulation, the common anticoagulants used for surgical patients, and recommendations for the use of epidural and spinal anesthesia in patients receiving anticoagulants.

Spinal and epidural anesthesia

A well-known complication of spinal and epidural anesthesia is hematoma formation. This can result from spontaneous bleeding or needle-induced damage to blood vessels.¹ Hemorrhage into the spinal canal most commonly occurs in the epidural space because of the prominent epidural venous plexus.² Because the area surrounding the spinal cord is a fixed space, any bleeding into the epidural space can cause spinal cord compression, neurological ischemia, and subsequent paralysis.³ Bleeding is less likely to become clinically significant in the intrathecal space because of the diluting effect of the cerebrospinal fluid.

- *Occurrence.* The risk of epidural hematoma is not considered a significant drawback of spinal and epidural anesthesia because of its rare occurrence.⁴ Tryba⁵ estimates that the overall incidence of epidural hematoma is 1:150,000 for epidural anesthetics and 1:220,000 for spinal anesthetics.^{1,5} In addition, in a retrospective analysis of the incidence of epidural hematoma with epidural anesthesia, Wulf⁶ found the incidence to be 1:190,000. Although these incidence data seem congruent, it should be considered that the incidence of epidural hematoma actually may be higher than reported in the literature due to the possibility of underreporting by anesthesia personnel.⁷ In cases in which a patient received anticoagulant medication during surgery, the estimated incidence of epidural hematoma is 33:100,000 for epidural anesthetics and 1:100,000 for spinal anesthetics, suggesting a relationship between anticoagulation during regional anesthesia and the development of a hematoma.⁸

- *Risk factors.* Risk factors for the development of

an epidural hematoma include anatomic abnormalities of the spinal cord or vertebral column, impaired hemostasis (pathological or drug-related), alcohol abuse, chronic renal insufficiency, vascular abnormalities, difficult needle placement, "bloody tap," and epidural catheter removal.^{1,2,9,10} Signs and symptoms of epidural hematoma include localized lower back pain followed by progressive motor and sensory deficits.^{3,6} The back pain also has been described as sharp and irradiating.⁷ Back pain may be thought of as the classic symptom for hematoma, but it may not always be present or the first symptom reported.^{7,10} Sensory and motor loss, including bowel and bladder dysfunction, numbness and tingling of the legs, muscle weakness, and paraplegia, may be the most common initial symptoms.⁷ Hematoma should be suspected if sensory or motor block outlasts the expected duration of the spinal or epidural anesthetic. Signs and symptoms of a hematoma may not be noted by the anesthesiologist and, therefore, diagnosis not made, particularly if the patient is diabetic (ie, impaired pain pathways), if the continuous-catheter technique is used and symptoms are masked, or if an ambulatory surgical patient notes symptoms of a hematoma only after discharge from the hospital.^{4,7}

- *Diagnostic testing.* When epidural hematoma is suspected, diagnosis can be confirmed by one or more tests. Magnetic resonance imaging is the preferred diagnostic tool, as it is considered to be the most sensitive.¹ Computed tomography scan is also an often-used diagnostic tool and may be more available and accessible. However, it has been noted that a computed tomography scan may miss smaller hematomas. A myelogram also may be used for diagnosis.¹⁰ Treatment of epidural hematoma consists of emergency decompressive laminectomy with evacuation of the hematoma.⁷ Overall, the outcome after epidural hematoma is poor.¹ A number of factors affect a patient's recovery from a hematoma, including the speed at which the hematoma develops, the severity of any preexisting neurological deficit, and the size and location of the hematoma. The most important factor in recovery is rapid decompression within 8 to 12 hours of symptom onset.³

Pharmacology of common anticoagulants

The following information is a review of common anticoagulants that the anesthesia provider may encounter in surgical patients. For each class of agents, the use, mechanism of action, and recommendations are discussed (Table).

- *Antiplatelet drugs.* Aspirin most often is administered as an analgesic, antipyretic, and antiplatelet drug for the prevention of thrombotic events.¹³ Aspirin blocks cyclooxygenase, which is responsible for the production of thromboxane A₂, a labile inducer of

Table. Recommendations for spinal and epidural anesthesia based on drug class^{11,12}

Drug class	Example drugs	Recommendations	Suggested laboratory tests
Antiplatelet agents	Aspirin/NSAIDs	None	None indicated
	Ticlopidine (Ticlid)	14 d before regional anesthesia	None indicated
	Clopidogrel (Plavix)	Discontinue 7 d before regional anesthesia	None indicated
	Eptifibatide (Integrilin); tirofiban (Aggrastat)	Avoid spinal and epidural procedures	None indicated
Oral anticoagulants	Warfarin (Coumadin)	Discontinue 4-5 d before regional anesthesia; monitor for 24 h postintervention*	Measure PT and INR before regional administration or removal of epidural catheter; INR should be < 1.5
Heparin	Subcutaneous heparin	Delay injection until after intervention* if possible	If > 4 d, assess platelet count
	Intravenous heparin	Delay administration 1 h after intervention*; catheter removal 2-4 h after last dose	Measure PT
LMWH	Ardeparin (Normiflo); dalteparin (Fragmin); enoxaparin (Lovenox); tinzaparin (Innohep); danaparoid (Orgaran)	Preoperative LMWH: regional administration 10-12 h after last dose; for higher doses, delay 24 h; for postoperative LMWH: (1) twice daily dosing: delay first dose 24 h; remove catheter and wait 2 hours before therapy initiation; (2) once daily dosing: first dose 6-8 h postoperatively; removal of catheter 10-12 h after last dose with subsequent dose 2 h after removal	None indicated
New anticoagulants	Bivalirudin (Angiomax); Lepirudin (Refludan)	Unknown; careful risk assessment	Monitor activated partial thromboplastin time
	Fondaparinux (Arixtra)	Use with extreme caution, only when atraumatic needle placement possible; avoid indwelling catheters	None indicated
Herbal medications	Garlic, ginkgo, ginseng, ginger, feverfew, vitamin E	Discontinue 5-7 d before surgery	None indicated

* Intervention indicates spinal administration, epidural catheter placement, or epidural catheter removal.

NSAID indicates nonsteroidal anti-inflammatory drug; PT, prothrombin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin.

platelet aggregation and a potent vasoconstrictor.¹⁴ The action of aspirin on platelets is permanent, lasting for the life of the platelet (7-10 days).¹⁴ In addition, long-term use of large doses of aspirin decreases prothrombin production, leading to a prolonged prothrombin time (PT).

Similar to aspirin, the nonsteroidal anti-inflammatory drugs (NSAIDs) exert their action by inhibiting cyclooxygenase and decreasing tissue prostaglandin synthesis.¹³ However, unlike aspirin, the effects of NSAIDs on platelets are reversible. Duration is dependant on the half-life of the specific drug and ranges from 1 hour to 3 days after the last dose.¹³

More recently developed antiplatelet drugs, ticlopidine and clopidogrel, commonly are used in patients at risk for cardiovascular and cerebrovascular thrombotic events.¹⁴ These drugs block the G_i-coupled platelet adenosine diphosphate receptor, resulting in a decrease in platelet activation.¹⁴ Inhibition of platelet aggregation persists for days after the drug is discontinued.¹⁴

Platelet glycoprotein IIb/IIIa receptor antagonists, eptifibatide and tirofiban, are used in the treatment of acute coronary syndrome.¹¹ These drugs reversibly inhibit platelet aggregation by preventing the binding of plasminogen, von Willebrand factor, and other adhesive ligands to glycoprotein IIb/IIIa.¹¹ Following

discontinuation of therapy, return of normal platelet aggregation occurs within 4 to 8 hours.¹¹

Although it is rare, Vandermeulen et al⁷ note that reports of epidural hematoma associated with spinal and epidural anesthesia and antiplatelet therapy exist. For this reason, the following general guidelines for the use of spinal and epidural anesthesia in the presence of antiplatelet therapy are offered. The ASRA does not offer specific recommendations regarding the timing of NSAIDs and spinal and epidural anesthesia or the timing of catheter removal in the presence of NSAIDs. The ASRA has concluded that NSAIDs alone do not represent any added significant risk to the development of epidural hematoma with spinal or epidural anesthesia.¹⁴ Vandermeulen et al⁷ suggest obtaining a bleeding time if aspirin has been taken 7 to 8 days or NSAIDs 1 to 3 days before surgery. However, although the bleeding time is proposed to be the best predictor of platelet function, a normal bleeding time does not guarantee normal platelet function.¹⁵ Furthermore, an abnormal bleeding time is not always indicative of inadequate hemostasis.¹⁵ Regarding the newer antiplatelet drugs, ticlopidine and clopidogrel, the ASRA has recommended discontinuation of ticlopidine for 14 days and clopidogrel for 7 days before spinal or epidural anesthesia. The ultimate decision regarding whether to use spinal or epidural anesthesia in the presence of antiplatelet therapy is to be made by the anesthetist only after careful assessment of the risks and benefits for each patient.

- *Oral anticoagulants.* Warfarin (Coumadin) is used in the prevention of venous and pulmonary thromboembolism, systemic embolism in patients with prosthetic heart valves or atrial fibrillation, stroke, and recurrent myocardial infarction.^{13,14} Warfarin inhibits vitamin K formation, resulting in depletion of vitamin K-dependent coagulation proteins (prothrombin; factors VII, IX, and X).¹³ The onset of warfarin is delayed for 8 to 12 hours, reflecting the presence of already circulating coagulation factors; however, peak effects do not occur for 36 to 72 hours.¹³ Likewise, after discontinuation, return of normal hemostasis may not occur for 1 to 3 days as evidenced by the return of the PT to 20% of normal.¹³

The ASRA has created the following recommendations for the use of oral anticoagulants with regional anesthesia: Long-term oral anticoagulation therapy should be stopped 4 to 5 days before surgery, and the PT and international normalized ratio (INR) should be measured before spinal or epidural anesthesia is given. In patients who receive their first dose of an anticoagulant before surgery, the PT and INR should be assessed if the dose was given more than 24 hours earlier or if a second dose has been administered. In patients receiving postoperative low-dose warfarin

therapy during epidural analgesia, the PT and INR should be monitored on a daily basis, and epidural catheters should be removed only when the INR is less than 1.5. In addition, it is beneficial to monitor the neurological status of patients for 24 hours after catheter removal to assess for signs and symptoms of epidural hematoma. Monitoring of neurological status should occur at least every 2 hours.

- *Standard heparin.* Heparin may be administered intravenously or subcutaneously for multiple purposes, most commonly to surgical patients for the prevention and treatment of venous thrombosis and pulmonary embolism.¹³ Heparin also is used commonly intraoperatively for anticoagulation for patients undergoing vascular and cardiovascular surgery. Heparin produces its anticoagulant effect by binding to antithrombin III, thus accelerating the normally occurring neutralization of thrombin and activated factors X, XII, XI, and IX.¹³ When administered intravenously, the average elimination half-life of 100 U/kg of heparin is 56 minutes; this will be prolonged with increases in dose and decreases in temperature.¹³

The ASRA offers the following recommendations for the use of heparin for patients receiving spinal or epidural anesthesia¹²: In patients receiving subcutaneous heparin, there is no contraindication to spinal or epidural anesthesia. Delaying the heparin injection until after the block may reduce the risk of bleeding, and the risk may be increased in debilitated patients or after long-term therapy.¹² Patients receiving subcutaneous heparin for longer than 4 days should have a platelet count assessed due to the risk of heparin-induced thrombocytopenia. Combining spinal or epidural anesthesia with anticoagulation during vascular surgery is appropriate, with the following precautions: (1) The technique should be avoided in patients with other coagulopathies. (2) The use of heparin should be delayed for at least 1 hour after needle placement. (3) If a catheter is to be removed, wait 1 hour after removal before administering subsequent doses of heparin, or wait 2 to 4 hours from the last dose of heparin before removal of the catheter. (4) Monitor patients receiving spinal or epidural anesthesia and heparin therapy postoperatively for signs and symptoms of hematoma. Other sources recommend that for the patient receiving preoperative intravenous heparin, regional anesthesia should be administered only after heparin has been discontinued for 3 to 4 hours and the prothrombin time or international normalized ratio has returned to normal.^{7,16}

- *Low-molecular-weight heparin.* Low-molecular-weight heparins (LMWHs) are derived from standard unfractionated heparin to yield fragments one third the size of heparin, resulting in a change in anticoagulant profile, pharmacokinetics, and effects on

platelet function.¹³ LMWHs have a lower affinity for antithrombin III than unfractionated heparin but maintain their effect on factor X; as a result, they do not alter the partial thromboplastin time.¹³ Current uses of LMWH include prophylaxis in surgical patients at risk for deep venous thrombosis and pulmonary embolism and treatment of unstable angina and non-Q-wave myocardial infarction.¹⁷ The half-life of LMWH is not dose-dependent and is 2 to 4 times that of standard heparin.¹⁶ Advantages of LMWH over standard heparin are the lower risk of bleeding complications and heparin-induced thrombocytopenia and the much greater bioavailability of LMWH.¹⁷

LMWHs were introduced in Europe in 1987 and in the United States in 1993.¹⁸ There was a noticeable increase in the incidence of spinal and epidural hematomas associated with neuraxial anesthesia and LMWHs compared with European data.² The greater margin of safety in Europe was related to differences in dosing guidelines for patients receiving neuraxial blocks. In the United States, since 1993, there have been more than 80 reports of epidural or spinal hematoma formation with concurrent use of enoxaparin and neuraxial anesthesia and spinal puncture.¹⁹ The majority of patients had an indwelling catheter for postoperative analgesia or received additional drugs affecting hemostasis.¹⁹

In an analysis of 60 cases of spinal hematoma reported to the US Food and Drug Administration (FDA), 40 cases were described through the MEDWATCH system between 1993 and 1998. Of these 40 cases, 2 patients received epidural steroid injections, 6 underwent spinal anesthesia, 23 had continuous epidural anesthesia, for 6 techniques were unspecified, and 2 had general anesthesia after attempted or failed neuraxial anesthesia.¹⁹ Emergency laminectomy was performed in 28 patients, and 16 had permanent paraplegia. On further review of the cases, additional risk factors for hematoma included difficulty in needle placement, administration of other antiplatelet or anticoagulant medication, timing of LMWH administration, and catheter removal.¹⁹ Reported incidences of spinal or epidural hematoma in patients receiving LMWH may be as high as 1 in 3,000 for continuous epidural anesthesia and 1 in 40,000 for spinal anesthesia.⁸ True estimates of frequency are difficult to determine due to voluntary reporting in safety surveillance databases.

Patient, anesthetic, and LMWH dosing variables associated with spinal hematoma have been proposed.¹⁵ The patient and anesthetic risk factors include female sex, older age, traumatic needle or catheter placement, epidural technique, and indwelling epidural catheter during LMWH administration. Variables related to LMWH dosing consist of immediate preoperative or intraoperative administra-

tion, early postoperative administration, concurrent antiplatelet or anticoagulant medications, and twice daily dosing.

The FDA issued a health advisory in 1997 and requested pharmaceutical companies to revise labeling of their respective products, specifically the placement of a boxed warning regarding the use of neuraxial anesthesia and LMWH.¹⁸ The warning clearly identifies the significant risk of hematoma that may result in long-term or permanent paralysis, caution with indwelling catheters, need for frequent monitoring, initiation of prompt treatment of symptoms, and benefit-risk assessment.²⁰

Recommendations for patients receiving LMWH in conjunction with spinal and epidural anesthesia are based on the avoidance of concurrent medications affecting coagulation, technical difficulties with regional block, and consideration of timing of regional block administration with thrombo-prophylaxis therapy.¹⁴ Potentiation of the anticoagulant effects of LMWH should be avoided through avoidance of the administration of other medications that affect hemostasis. During needle and catheter placement, the presence of blood does not necessitate postponement of the surgical procedure. LMWH administration should be postponed for 24 hours postoperatively. If traumatic needle and catheter placement occurs, there may be a significant increased risk for hematoma formation. The decision to proceed with surgery and subsequent LMWH therapy is based on careful assessment of the patient risks and benefits and communication with the surgeon.

- *Preoperative LMWH.* Patients receiving preoperative LMWH therapy are assumed to have altered coagulation.¹⁴ Spinal and epidural anesthesia should occur 10 to 12 hours after the last dose of LMWH. For patients receiving higher doses of LMWH, needle insertion should be delayed for at least 24 hours. If a prophylactic dose of a LMWH is administered 2 hours before surgery, spinal and epidural anesthesia should be avoided because needle placement likely would occur during peak anticoagulant activity.

- *Postoperative LMWH.* Optimal management of patients scheduled to receive postoperative LMWH therapy includes consideration of timing of therapy, dosing schedule, and the presence of an indwelling catheter. In patients receiving twice daily dosing, the first dose of LMWH should be administered 24 hours postoperatively. Indwelling spinal and epidural catheters should be removed before initiation of therapy. If a continuous regional technique is used, the catheter can be left in overnight and removed the following day. The patient should not receive LMWH until 2 hours after the neuraxial catheter has been removed.

In patients receiving once daily dosing, the first dose of LMWH should be given 6 to 8 hours postoperatively. The second postoperative dose should be administered no earlier than 24 hours after the first dose. Indwelling neuraxial catheters may be safely maintained, and removal should occur a minimum of 10 to 12 hours after the last LMWH dose. Subsequent dosing should occur a minimum of 2 hours after catheter removal.

- *New anticoagulants.* Drugs affecting various components of the coagulation system are continually under development. The new anticoagulants include thrombin inhibitors such as bivalirudin used in interventional cardiology and lepirudin used to treat heparin-induced thrombocytopenia. Due to limited information, caution is advised regarding selection of anesthetic technique. Recommendations for administering spinal and epidural anesthesia to these patients includes careful assessment of risk factors associated with bleeding.¹⁴

Fondaparinux (Arixtra) is a new antithrombotic drug used for prophylaxis of deep venous thrombosis in patients undergoing hip fracture or replacement surgery or knee replacement surgery.²¹ Fondaparinux exerts its action by selective inhibition of factor Xa, mediated through antithrombin III.²¹ By selectively binding antithrombin III, the innate neutralization of factor Xa is potentiated by 300 times. Peak effect occurs in 3 hours, and the elimination half-life is 17 to 21 hours.²¹

The FDA has issued a black box warning for the use of fondaparinux with spinal and epidural anesthesia similar to the warning mentioned for LMWH. The actual incidence of spinal and epidural hematoma is unknown.¹⁴ The ASRA states that extreme caution is warranted due to the sustained antithrombotic effects, early postoperative dosing, and irreversibility of the effects of fondaparinux. Spinal or epidural anesthesia should be used only when a single-needle pass with atraumatic needle placement is possible. Furthermore, indwelling catheters should be avoided.

- *Herbal medications.* The use of herbal medicines by the perioperative surgical population has been reported to be between 22% and 51%.²² One noted side effect of herbal medications is bleeding. Herbal medications can affect coagulation through a variety of mechanisms, including the following:

- Inhibition of platelet aggregation (garlic, ginger, feverfew)
 - Antiplatelet components (ginseng)
 - Coumarin component (alfalfa, chamomile, horse chestnut, ginseng)
 - Reduction of platelet thromboxane production (vitamin E)
 - Inhibition of platelet-activating factor (gingko)
- Many patients taking herbal products are unaware of

the potential drug interactions with over-the-counter and prescription anticoagulant medications. The potential for bleeding is increased with coadministration of other anticoagulants such as NSAIDs, warfarin, aspirin, and LMWH. Long-term use of herbal medications affecting coagulation is of concern for the anesthesia provider when administering spinal or epidural anesthesia to these patients. The potential risk for the development of spinal and epidural hematoma is unknown.

Debate and controversy exist as to the discontinuation of herbal medications preoperatively. Careful preoperative assessment of the patient to identify alterations in health that may contribute to bleeding is crucial. Most surgical patients are advised to discontinue the use of all herbal products at least 5 to 7 days preoperatively.²³

State of the art

Specific recommendations have been discussed for each drug class mentioned. However, the ASRA also offers general statements that may be broadly applicable regarding the perioperative use of anticoagulants and regional anesthetic techniques⁵: (1) Concurrent use of other medications that alter coagulation may increase the risk of bleeding without altering the results of coagulation studies. (2) For patients with an indwelling catheter who are at an increased risk for epidural hematoma, an opioid or dilute anesthetic solution should be used postoperatively to minimize the degree of sensory and motor block, allowing for accurate neurological assessment. (3) Epidural catheters should be removed at the nadir of anticoagulant therapy, and subsequent doses should not be given immediately following catheter removal. (4) Frequent evaluation of motor and sensory function to allow for early detection of epidural hematoma should be carried out. (5) In very-high-risk cases, continued monitoring of neurological function should be done for at least 24 hours after epidural catheter removal.

Summary

Controversy over the use of spinal and epidural anesthesia in patients receiving anticoagulants is ongoing due to the potential risk for epidural hematoma. In patients who develop a hematoma following spinal or epidural anesthesia, the outcome can be devastating and permanent. Therefore, anesthetists should follow practice guidelines based on scientific data and have a sound knowledge base of the anticoagulant drugs to make an informed decision regarding the use of spinal or epidural anesthesia. A thorough preoperative assessment, including recent drug therapy and bleeding history, is essential. When a patient taking anticoagulant medications is encountered, the benefits vs the risks of regional anesthesia must be considered

seriously. If the decision is made to use spinal or epidural anesthesia for these patients, continuing postoperative surveillance, communication, and education of attending physicians and nurses are crucial to avoid a disastrous outcome.

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