Perioperative Low-Molecular-Weight Heparin and Neuraxial Anesthesia: A Review of Current Practice Guidelines

D Cannavo, R Friedman

Citation

Abstract
Over the past nine years, the wide acceptance of low-molecular-weight heparins (LMWHs) in the United States has been the result of this class of drugs excellent safety and efficacy profile across multiple applications to prevent and treat arterial and venous thromboembolic disease. There has been concern, however, about the safety of using anticoagulant-based deep vein thrombosis (DVT) prophylaxis with regional anesthesia. This concern arose from a number of case reports in which the development of spinal hematomas was linked to the administration of LMWHs in patients receiving concomitant neuraxial anesthesia. In December 1997, the FDA issued an advisory about these adverse events indicating that there might be a relationship between epidural hematoma and neuraxial anesthesia in patients receiving LMWHs. Manufacturers of LMWHs subsequently added a boxed warning to their prescribing information alerting clinicians to these potential effects. Subsequently, the American Society of Regional Anesthesia (ASRA) produced guidelines with respect to the safe use of anticoagulants in patients receiving neuraxial anesthesia/analgesia based upon the available case reports and evidence. Upon review of the data, the inherent efficacy and widespread acceptance of LMWHs for prophylaxis of DVT, it may be concluded that conscientious use of LMWHs and neuraxial anesthesia may be provided safely in nearly every situation if attentive towards proper administration relative to the use of anesthesia.

The fact that regional anesthesia reduces the risk of venous thromboembolism when other pharmacologic prophylaxis is not used after joint replacement surgery is well documented (Table 1). Further, it is recognized that in joint replacement, clot formation begins intraoperatively. Thus the use of neuraxial anesthesia and post-operative analgesia combined with early pharmacologic prophylaxis would appear to be the most efficacious approach toward preventing thromboembolic complications. The purpose of this review is to summarize the proper guidelines for the management of patients undergoing joint replacement surgery in the context of pharmacologic DVT prophylaxis and neuraxial anesthesia and analgesia.

Figure 1
Table 1. Comparative Influences of Epidural and General Anesthesia on Deep Vein Thrombosis and Pulmonary Embolism after Total Hip Replacement (no antithrombotic drug prophylaxis used)

<table>
<thead>
<tr>
<th>Event</th>
<th>Continuous Epidural Block (n = 15)</th>
<th>General Anesthesia (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>PE</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>


THROMBOSIS AND REGIONAL ANESTHESIA

It is important to consider the relationship between the reduction of thromboembolic complications and the use of regional anesthesia. It has been shown that deep venous thrombosis (DVT) can be reduced by approximately 50% with the use of regional anesthesia in joint replacement surgery when other forms of pharmacologic prophylaxis are not used (Table 2). A retrospective meta-analysis of 141 studies involving 9,559 patients, reported in December 2,000, demonstrated that DVT, pulmonary embolism (PE), transfusion and pneumonia were all reduced in patients receiving a neuraxial anesthetic combined with general anesthesia. Mortality was one-third lower in patients receiving a neuraxial anesthetic alone.
Perioperative Low-Molecular-Weight Heparin and Neuraxial Anesthesia: A Review of Current Practice Guidelines

Figure 2
Table 2. Effects of Neuraxial Blockade (NB) on Post-Operative Complications (vs General Anesthesia)

<table>
<thead>
<tr>
<th>Event</th>
<th>NB (n = 4,377)</th>
<th>No NB (n = 9,920)</th>
<th>Odds Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Vein Thrombosis</td>
<td>145</td>
<td>220</td>
<td>44</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>29</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>45</td>
<td>59</td>
<td>33</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>149</td>
<td>238</td>
<td>36</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>26</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Peri-Operative Transfusion</td>
<td>103</td>
<td>280</td>
<td>59</td>
</tr>
<tr>
<td>Peri-Operative Bleed</td>
<td>51</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>Post-Operative Mortality</td>
<td>103</td>
<td>144</td>
<td>38</td>
</tr>
</tbody>
</table>


O’Hara, et al. published a prospective study on the effect of anesthetic technique in hip fracture patients. The investigators examined the effect of general versus neuraxial anesthesia on the incidence of myocardial infarction, congestive heart failure, pneumonia, and confusion; and concluded that anesthetic technique had no effect on outcome. It is important to note that the former study, even considering the limitations of a retrospective meta-analysis, was for all ages and all types of procedures, which may select out co-morbidities. In contrast, O’Hara, et al. studied hip fracture patients only, which tend to be older and as a result have increased co-morbidities.

In terms of mechanism, regional anesthesia seems to derive its anti-thrombotic effect by the attenuation of the surgical stress response, one component of which is sympathetic vascular tone (Table 3). By blocking vascular tone, venous stasis and an environment conducive to clot formation is undermined (Figure 1). Beyond reducing stasis, regional anesthesia facilitates intraoperative hypotension. This creates an optimized surgical field and permits a more efficient surgical procedure. Longer operations have been associated with increased complications including DVT, bleeding and infection. Specifically, the overall rate of DVT formation was 10% in operations lasting less than 70 minutes and 20% in operations lasting greater than 70 minutes. Hypotensive anesthesia alone may itself be a useful modality in the prevention of DVT. Excessive bleeding during normotensive anesthesia necessitates the administration of IV fluids, which may dilute anti-thrombin III levels creating a prothrombotic state. Finally, intraoperative regional anesthesia allows for post-operative neuraxial analgesia. Acutely post-operatively this eliminates the sympathetic response to pain in the PACU and thus systolic hypertension, resultant bleeding and the need for transfusion.

Neuraxial analgesia promotes early ambulation, which further reduces venous stasis and therefore provides a less thrombogenic environment.

Figure 3
Table 3. Advantages of Regional Anesthesia

<table>
<thead>
<tr>
<th>Intra-Operative</th>
<th>Autonomic Nervous System</th>
<th>Anticoagulant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine/Metabolic</td>
<td>Anticoagulant Therapy</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Catecholamines</td>
<td>α-ACTH</td>
</tr>
<tr>
<td>α-Fenoldylamide</td>
<td>α-Fenoldylamide</td>
<td>α-Fenoldylamide</td>
</tr>
<tr>
<td>α-Hemoldylamide</td>
<td>α-Hemoldylamide</td>
<td>α-Hemoldylamide</td>
</tr>
<tr>
<td>β-Fenoldylamide</td>
<td>β-Fenoldylamide</td>
<td>β-Fenoldylamide</td>
</tr>
<tr>
<td>β-Hemoldylamide</td>
<td>β-Hemoldylamide</td>
<td>β-Hemoldylamide</td>
</tr>
<tr>
<td>Post-Operative</td>
<td>Anticoagulant Therapy</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>Endocrine/Metabolic</td>
<td>Anticoagulant Therapy</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Catecholamines</td>
<td>α-ACTH</td>
</tr>
<tr>
<td>α-Fenoldylamide</td>
<td>α-Fenoldylamide</td>
<td>α-Fenoldylamide</td>
</tr>
<tr>
<td>α-Hemoldylamide</td>
<td>α-Hemoldylamide</td>
<td>α-Hemoldylamide</td>
</tr>
<tr>
<td>β-Fenoldylamide</td>
<td>β-Fenoldylamide</td>
<td>β-Fenoldylamide</td>
</tr>
<tr>
<td>β-Hemoldylamide</td>
<td>β-Hemoldylamide</td>
<td>β-Hemoldylamide</td>
</tr>
</tbody>
</table>


RISKS OF SPINAL AND EPIDURAL HEMATOMAS

The incidence of neurologic sequelae following hemorrhagic complications related to neuraxial block is not definitively known, although it is estimated to be <1/150,000 after epidural anesthesia and <1/220,000 in spinal anesthesia. Thus, there is a risk of epidural hematoma formation from simply having instrumented the epidural space. Spinal hematoma may also occur in the presence of other pre-existing vascular pathologies, especially with neoplastic disease or in conjunction with antiplatelet or anticoagulation therapy. Bleeding complications following neuraxial block may be especially serious, because the spinal canal is an enclosed space and the bleeding may be occult. The result of such an adverse event may include neurologic ischemia and both transient and permanent paraplegia.

As previously stated, spinal hematoma may occur spontaneously, with or without the presence of antiplatelet or anticoagulation therapy. In fact, there were 199 case reports of spontaneous epidural hematoma, 24% with oral anticoagulation, prior to 1993 when LMWHs were first approved for use in the US. Several large studies have documented the safety of the perioperative use of anticoagulant therapy in the context of neuraxial anesthesia.

Patients under general anesthesia may also rarely experience spontaneous spinal hematomas. One report described a subdural hematoma in a patient who underwent a gastric...
perioperative low-molecular-weight heparin and neuraxial anesthesia: a review of current practice guidelines

3 of 10

resection under general anesthesia and received preoperative anticoagulation with a LMWH. With respect to the case reports presented at the ASRA consensus conference, it is important to note that in many of the cases, there was no relationship between timing of anesthetic intervention and dosing of the LMWH. Specifically, some epidural catheters were placed or removed when the anticoagulant activity of the drug was highest (Table 4).

Figure 4
Table 4. Case Reports: Enoxaparin and Spinal Hematoma

CHARACTERISTICS OF SUSCEPTIBLE PATIENTS

Several studies have helped better identify patients who may be more susceptible to spinal hematoma during a neuraxial block. One study presented a broad review of the literature from 1906 to 1994, finding 61 cases of spinal hematoma following spinal or epidural anesthesia. The review identified nine patients who presented with various anatomic abnormalities, including spina bifida occulta, spinal angioma, ankylosing spondylitis, spinal ependymoma, and vascular malformations. Most notably, fully 42 patients demonstrated some evidence of impaired hemostasis: 12 had coagulopathy, thrombocytopenia or were treated with either antiplatelet medications such as aspirin, ketorolac, oral anticoagulants like phenprocoumon, thrombolytics such as urokinase, or Dextran 70 directly before or after the spinal or epidural anesthesia.

The review revealed that 32 patients received an epidural anesthetic via an indwelling catheter. Of these 32 patients, 15 (47%) experienced spinal hematomas directly following the removal of the catheter, suggesting that both the patient’s coagulation status and catheter removal are important factors in the development of spinal hemorrhage. The study also found that needle placement was felt to have been difficult and/or bloody in 25% of patients, with multiple punctures required in 20% of patients. The study concluded by noting that fully 87% of patients either exhibited impaired hemostasis or difficulty in needle placement.

It is noteworthy that in this study and in another literature review, 75% of the 40 cases of spinal hematoma were in women, with a median age of 75 years. This finding is echoed in another study that reviewed the characteristics of patients who had experienced minor hemorrhagic complications-defined as blood present during needle or catheter placement-following neuraxial block. The study found that female gender, advanced age (i.e., ≥65 years), and a history of easy bruising significantly predisposed patients to hemorrhagic complications.

PATIENT MANAGEMENT

The real benefits of regional anesthesia must be considered against the small but real risk of spinal hematoma in patients undergoing neuraxial block who receive anticoagulants, antiplatelet therapy or thrombolytics. Judgment should be made on an individual basis, starting with a detailed bleeding history. Patients should be asked about the presence of an inherited bleeding disorder and whether they have ever experienced unusual bleeding following surgery or trauma. Clinicians should inquire about central nervous system bleeding, dental extraction bleeding, ecchymoses, epistaxis, gingival bleeding, hemarthroses, hematemesis, hematochezia, deep muscle hematoma, hematuria, hemoptyysis, melena, petechiae, and abnormal menstrual or obstetrical bleeding in women.

The anesthesiologist should be aware that certain medical conditions—excluding chronic liver or renal disease, intestinal malabsorption diseases, disseminated intravascular coagulation, acquired factor deficiencies and inhibitors, and platelet dysfunctions of various kinds could cause abnormal bleeding. The surgeon and the anesthesiologist should proactively communicate on the plan for anesthesia and analgesia with that of thrombosis prevention. The clinicians should know of any previous transfusions and any concomitant anticoagulation or factor replacement therapy.

With respect to post-operative management, dilute local
anesthetic agents are recommended for continuous epidural to allow for neurologic monitoring while still providing analgesia. Monitoring for signs of cord compression in the peri-operative period is crucial with the typical initial complaint being new-onset weakness or numbness, not severe radicular back pain, as one might suspect. The first neuromuscular symptom of spinal hematoma was muscle weakness in 46% of patients and sensory deficit in 14% of patients in the work performed by Vandermeulen.16

When spinal hematoma is suspected, an evaluation should be carried out with an MRI scan immediately. Upon confirmation, the treatment of choice remains emergency decompressive laminectomy. Note that recovery is increasingly unlikely with time, and studies caution against waiting more than 8 to 12 hours to perform corrective surgery.

**DRUG INTERACTIONS**

Anticoagulants can elicit a variety of responses among patients, with some demonstrating a pronounced anticoagulant effect, with prolongation of the prothrombin time. Others show resistance to anticoagulants, with blunted effects that return to normal more readily. Factors that affect sensitivity to heparin and warfarin include renal function, diet, presence of liver disease and general medical condition. Medications such as nonsteroidal anti-inflammatory drugs taken concomitantly may alter the effect of anticoagulants.

Considering warfarin specifically, both diet and concomitant medications are exceedingly important. Warfarin exerts its effect by interfering with the synthesis of vitamin K dependent cofactors. As vitamin K is synthesized by gut flora, anything that affects gut flora such as diet and antibiotics can decrease vitamin K levels and result in an exaggerated and rapid response to warfarin. Further, warfarin is 95% protein bound and most other drugs including non-steroidal displace it resulting in increased bioavailability and thus an exaggerated response. This is particularly relevant in the elderly in whom diet is variable, who are often on many medications and who comprise the majority of joint replacement patients. Further, antibiotics are an integral component of the management of total joint patients. The anesthesiologist in particular must therefore be thoroughly versed in the patient’s overall medical status and attuned to the possible effects that might result from these conditions.

**BIOCHEMISTRY OF LMWH**

A short background in the pharmacokinetics and pharmacodynamics of LMWH is necessary to understand the rationale from which practice guidelines were generated. It is important to understand that each LMWH is different from the other and are not interchangeable.18,19,20

LMWHs have bioavailability of greater than 90% following subcutaneous administration. This predictable anticoagulant response is realized with fixed prophylactic doses, as well as, treatment doses adjusted for weight. This means that monitoring anticoagulant response using anti-Xa levels is not necessary, as concluded by the consensus participants and others.21,22

Clearance of LMWH is largely renal. The anticoagulant response to LMWH administration, as seen in anti-Xa levels, peaks 3-4 hours after subcutaneous administration. The half-life of LMWH is 3-4 times and the plasma half-life is 2-4 times that of standard heparin, so some anti-Xa activity remains even 12 hours post-injection although at prophylactic doses this is less than 10% and not clinically significant. The anticoagulant effect of standard heparin is reversed following an equimolar injection of protamine. However, only the anti-IIa activity of LMWH is completely reversed following protamine administration.

**NEURAXIAL BLOCK AND LMWH**

The safety and efficacy of LMWH for postoperative prophylaxis against venous thromboembolism has been confirmed in more than 60 clinical trials, involving more than 20,000 patients.23 Nonetheless, accumulated reports of spinal hematoma have focused concern on the overall safety of spinal and epidural anesthesia in patients taking LMWH.

Horlocker and Wedel21 examined 40 cases of spinal hematoma that were associated with the administration of LMWH. Each of these cases had been reported to the Food and Drug Administration’s (FDA) MedWatch reporting system, a program instituted to detect unusual or unexpected adverse drug events. MedWatch relies on reports sent to the FDA by clinicians, hospitals and drug manufacturers. A full analysis of the 40 cases cannot be made as most of the cases had been reported to MedWatch with relatively brief descriptions of events; only two of the incidents have been published as case reports. Importantly, there are no comparative data of the millions of patients who received LMWH and neuraxial anesthesia uneventfully. The authors noted that about three-quarters of the 40 spinal hematoma
cases occurred in elderly women indicating this may be a population at increased risk for these serious adverse reactions.\textsuperscript{21}

Spinal hematomas occurred in patients receiving both single-dose and continuous neuraxial anesthesia. Anesthetic techniques in the 40 cases of spinal hematomas were described as: general anesthesia following failed neuraxial block in three patients; epidural steroid injection in two patients; spinal anesthesia in six patients, which includes one continuous spinal technique; continuous epidural anesthesia in 23 patients; unspecified continuous technique in two patients; and unspecified technique in the remaining four patients.\textsuperscript{21}

Horlocker and Wedel\textsuperscript{21} evaluated those cases in which neuraxial techniques were unsuccessful together with single dose techniques, reasoning that any trauma to the vasculature of the spinal canal would have occurred during needle placement, whether successful or not. They found that each of these patients had at least one risk factor for spinal hematoma: difficult needle placement, concomitant anticoagulation therapy, or early administration of LMWH before the recommended 12 to 24 hour postoperative period. Noting the number of patients in whom needle placement must be abandoned has been historically small. The authors found that the three cases of spinal hematoma in patients whose needle placement had to be abandoned were significant.\textsuperscript{21} This suggests that prolonged needle trauma places the patient at increased risk.

The remaining 26 patients received some type of continuous neuraxial technique: spinal in one, epidural in 23, or unspecified continuous in two. Of these, the actual timing of LMWH administration was known in 20 patients. Of this group, four patients received LMWH preoperatively; 11 received LMWH within 12 hours of catheter placement; seven patients were receiving concomitant antiplatelet medications; two received warfarin.\textsuperscript{21}

The timing of the onset of symptoms was known in 21 patients.\textsuperscript{21} Of this group, four patients experienced symptoms while the catheter was in place; seven patients reported symptoms within a few hours of catheter removal; 10 patients reported no symptoms for 12 hours or more after catheter removal. The median time from initiation of LMWH therapy and recognized neurologic dysfunction was three days in these cases, and the median time to onset of symptoms and eventual laminectomy was more than 24 hours. Whether the increased incidence of spinal hematoma in patients with indwelling catheters is due to the level of anticoagulation from the twice daily dosing regimen or the timing of catheter removal is impossible to determine since only six case records included information on the timing of LMWH dosing and catheter removal.\textsuperscript{21}

GUIDELINES FOR THE USE OF LMWH IN NEURAXIAL ANESTHESIA/ANALGESIA

Enoxaparin has been shown to be a safe and effective means of DVT prophylaxis in terms of compliance, outcome and cost.\textsuperscript{23,24,25,26,27,28} It is also clear that choice of anesthetic is an integral part of a combined approach to DVT prophylaxis. With consideration of the following guidelines, it can be concluded that both spinal and epidural anesthetics can be safely administered with pharmacologic DVT prophylaxis with enoxaparin.

The “Consensus Conference on Neuraxial Block and Anticoagulation “ was convened on May 2-3, 1998 in Chicago, and included experts on regional anesthesia, hematology/thromboprophylaxis, orthopedic surgery, and epidemiology. What follows is an overview of the recently released findings of the consensus conference, which concern the use of LMWHs during neuraxial anesthesia. To provide additional information, a brief summary of the European practice guidelines will first be reviewed.

OVERVIEW OF LMWH USE IN EUROPE

Since LMWH was first approved for use in Europe, experience and clinical studies pre-date those available in the United States. The principal examination of the use of LMWH in patients receiving spinal or epidural anesthesia was undertaken by Bergqvist et al.\textsuperscript{30,31} These investigators reviewed European studies and identified 9,013 patients who had received a combination of LMWH and neuraxial anesthesia, and found that complications attributable to LMWH were extremely rare.

European practice guidelines for the use of LMWH and neuraxial anesthesia emerged with experience, and include:
1) delay needle placement 8-12 hours after dose of LMWH;
2) delay administration of LMWH 8-12 hours following needle placement; 3) traumatic needle placement necessitates delay of LMWH or substitute thromboprophylaxis; and 4) catheter removal is allowed 8-12 hours after LMWH administration or 1-2 hours before the next dose.
The difference in the European experience and frequency of spinal hematoma may be partially attributable to dosage differences. Enoxaparin dosing for hip and knee replacement surgery, for instance, has been 30 mg (3000 U) every 12 hours subcutaneously in the United States (for up to 14 days), whereas in Europe the dose is 40 mg (4000 U) once daily. However, enoxaparin now offers this flexibility in the United States, with European-style dosing approved for hip replacement surgery. The 40 mg qd S.C. dosing is recommended 12 hours preoperatively and then continuing for 3 weeks as prophylaxis. The European regimen may provide less anticoagulation and a greater diminution of heparin activity over time than its U.S. counterpart. The timing of the initial dose in orthopedic patients also varies, with LMWH administered 12 hours preoperatively in Europe and 12-24 hours postoperatively in the United States.

Variations in regional anesthetic technique may also play a role, because only 5 of the 40 patients suffering spinal hematomas had undergone single-dose spinal anesthesia. Estimates of the past (pre-consensus) frequency of spinal hematoma in patients receiving LMWH have been figured at 33:100,000 in those undergoing epidural technique and 1:100,000 in those receiving spinal anesthesia. The European results are interesting, particularly because European usage includes preoperative dosing at 40 mg once daily. This may in fact be a good approach, because DVT may tend to form intraoperatively. By administering LMWH preoperatively, the Europeans guidelines are addressing this issue. One conclusion is hard to refute: The adoption of the European guidelines has been successful in limiting the frequency of spinal hematoma in those patients receiving perioperative LMWH and neuraxial anesthesia. The presence of and success with the European guidelines was noted and evaluated by the consensus participants. However, the European experience is not without criticism as some consensus participants felt that the frequency of spinal hematomas in Europe may be higher than that reported in the literature.

GUIDELINES FOR REGIONAL ANESTHESIA AND LMWH IN PATIENTS REQUIRING PROPHYLAXIS.

The use of LMWH with spinal and epidural anesthesia is safe as long as published guidelines and recommendations from experienced clinical authorities are observed. Single-shot spinal anesthesia with preservative-free morphine and epinephrine provides good anesthesia and postoperative analgesia while minimizing risk of epidural hematoma formation. Perhaps most important, local anesthetics in epidural injections potentially can interfere with the neurologic examination by causing some mild numbness or weakness. The ASRA consensus conference addressed this by encouraging anesthesiologists to minimize the concentration of local anesthetic in the anesthetic solution. This may, however, be a recommendation that is more theoretical than practical (Table 5).

Table 5. ASRA Recommendations for Perioperative LMWH and Neuraxial Anesthesia. (A full review of the conference can be found in “Regional Anesthesia and Pain Medicine”.)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant causing bleeding risk</td>
<td>Administration of other anticoagulant or oral anticoagulant medications in combination with LMWH presents an added risk of perioperative hemorrhagic complications including spinal hematoma. It is important to note that Con-A inhibitors have no effect on platelet function.</td>
</tr>
<tr>
<td>Blood pressure 24 hour delay</td>
<td>Blood pressure and heart rate should be monitored closely for 24 hours after the administration of LMWH.</td>
</tr>
<tr>
<td>Pre-op LMWH delay after completion of epidural placement</td>
<td>Delay needle placement. Needle placement in these patients should occur 12-24 hours after the administration of LMWH.</td>
</tr>
<tr>
<td>Post-op LMWH delay prior to initiation of LMWH therapy</td>
<td>Assure patients receiving prophylactic LMWH have altered coagulation. Needle placement in these patients should occur 12-24 hours after the administration of LMWH.</td>
</tr>
<tr>
<td>Administer LMWH post-op</td>
<td>Patients receiving single dose anesthesia or via continuous catheter may receive LMWH initiated postoperatively. The first dose should be administered no earlier than 24 hours postoperatively and only in the presence of normal vital signs.</td>
</tr>
</tbody>
</table>

Catheter removal is another important consideration in epidural anesthesia. Catheter removal has been documented to be a traumatic event. According to the ASRA guidelines, one must wait at least 10 to 12 hours after the last dose of LMWH to withdraw the catheter and then wait another 2 hours before giving the next LMWH dose.

In general, either the catheter should be removed at the end of the surgery and LMWH prophylaxis should begin 12 to 24 hours later, or the catheter should be removed early in the morning (e.g., 7 AM) on the day after surgery and LMWH
therapy should begin 2 hours later. When LMWH therapy is begun with the catheter still in place, it is advisable to skip one dose of LMWH before removing the catheter. It is not advisable to have an epidural catheter in place at treatment doses (i.e., 1mg/kg bid of enoxaparin).

If a traumatic epidural or spinal injection occurs, special precautions must be observed when administering LMWH. This event was disproportionately represented in the case reports considered by the ASRA consensus conference. When a regional technique is attempted but abandoned for general anesthesia, patients probably sustain excessive trauma to the epidural space. In this situation, it is better to wait at least 24 hours before initiating LMWH therapy.

THE IMPORTANCE OF TECHNIQUE

Several studies have pinpointed technique as an important factor in cases of spinal bleeding. Vandermeulen et al. found that catheter removal was significant in the development of spinal bleeding. Other studies have concluded that the placement of an indwelling intrathecal or epidural catheter increases the risk of minor spinal bleeding. One such study explored the trauma associated with an indwelling 22-gauge intrathecal catheter. This study followed 20 arthroplasty patients (receiving 2000 to 4000 U enoxaparin), 22 vascular patients (receiving 100 U/kg I.V. heparin intraoperatively) and 24 prostatectomy control patients (receiving no anticoagulant or antiplatelet therapy). They found 10 arthroplasty or vascular patients and seven controls who had more than 100 x 10^3/L erythrocytes and/or blood-tinged CSF.

While most clinicians should consider both spinal and epidural anesthesia to be safe in the context of LMWHs, a spinal anesthetic can be used in the majority of cases. First, if there is a large volume of cases, spinal anesthesia is more efficient as epidurals take more time to place and achieve surgical anesthesia. Second, epidurals require a higher level of nursing involvement. With respect to the anesthesia itself, the lack of a local anesthetic infusion in a spinal allows for an optimized neurologic exam. Also, placing an epidural catheter involves a larger needle and not only threading but also withdrawing an epidural catheter subjects the epidural space to trauma. Thus, it is better to reserve continuous epidural catheters for pelvic trauma patients and complicated revision joint replacements. Enoxaparin can be safely initiated with catheters in place. In this circumstance, enoxaparin is held in the evening and catheters discontinued the following morning. This creates a 24-hour window for true normalization of coagulation. Enoxaparin can be restarted 2 hours after catheter removal.

Whichever modality is chosen, needle and catheter placement must be as atraumatic as possible. The ASRA Consensus Conference recommends the use of small-gauge spinal needles and suggests minimizing catheter insertion distances to 3-4 cm to decrease trauma to epidural vessels. As stated above, in cases of traumatic placement of a spinal or epidural and more specifically in cases of abandoned neuraxial technique, there is an increased risk of spinal hematoma and it is advisable to wait 24 hours before initiation of LMWH therapy.

MONITORING

In accordance with the ASRA and ACCP guidelines, the only monitoring necessary for patients being treated with LMWH is measurement of platelet count, usually as single measurement. Heparin-induced thrombocytopenia, although much less common with LMWHs than with unfractionated heparin, is still a concern. All heparin-based products should be avoided in patients with a documented history of heparin-induced thrombocytopenia.

Monitoring anticoagulation during warfarin therapy is more complex. It requires following the prothrombin time (PT) or INR, which is expensive and time consuming. An important point, however, is that PT/INR does not precisely reflect the anticoagulant activity of warfarin. In the coagulation cascade, the initial prolongation of the PT is due to inactivation of factor VII, which has a short half-life, 7 hours. The therapeutic effect of warfarin, however, derives from inactivation of factors II and X with half-lives of 48 and 72 hours respectively. Thus, the clinical activity of warfarin lags behind its laboratory effect. Furthermore, when warfarin is discontinued, the PT begins to normalize as factor VII activity returns but the therapeutic effect remains until factors II and X are corrected.

According to the ACCP guidelines, warfarin may be used preoperatively. The ASRA consensus conference recommendation is to monitor the PT prior to initiating neuraxial block. For the reasons outlined above, initial dosing of warfarin can be unpredictable and thus problematic. Moreover, until catheter removal, it must also be checked on a daily basis and again, onset of action can be unpredictable and one my find themselves with a therapeutic INR and an epidural catheter in place. At this point the only options are vitamin K and or FFP after which the redosing of
warfarin is very difficult.

**DISCUSSION**

Physicians using LMWH combined with neuraxial block anesthesia may feel confident in terms of efficacy and safety. Clinical studies to reaffirm the safety and efficacy of this approach continue. The results from one such study were presented in February 1999 at the annual meeting of the American Academy of Orthopedic Surgeons. The study reviewed the outcome of 487 total joint patients who received enoxaparin for DVT prophylaxis. Of these, 256 underwent total hip replacement (208 primary, 48 revision) and 231 underwent total knee replacement (204 primary, 27 revision). The patients consisted of 238 women and 149 men aged 18-92. Diagnoses included osteoarthritis (344), rheumatoid arthritis (31), avascular necrosis (20), post-trauma (6) and miscellaneous others.

The protocol required starting enoxaparin prophylaxis 12 hours postoperatively at 30 mg bid. General anesthesia was provided for 234 patients and spinal anesthesia was given to 253 patients. There were no spinal hematomas or any other serious complications related to neuraxial anesthesia. There were four nonfatal pulmonary emboli and one case of DVT in the 487 patients, for an incidence of 1.03%. Bleeding complications were also rare. Transfusions over two units were required in 3.7%; wound hematomas, 0.4%; wound drainage lasting more than 5 days, 13.3%; gastrointestinal bleeding, 0.8%; and platelet counts <100,000 resolving spontaneously, 2.9%. The administration of enoxaparin was discontinued by the physician in 3.7% of patients.

This study clearly demonstrates that enoxaparin is safe and effective, and remains so even when employing neuraxial anesthesia technique. As long as enoxaparin and the other LMWH drugs are used in accordance with the guidelines generated by the ASRA in the May 1998 Consensus Conference, then neuraxial anesthesia can be used in the context of pharmacologic DVT prophylaxis.

**CONCLUSION**

As a class, LMWH drugs have revolutionized DVT prophylaxis and treatment in orthopedic surgery, general surgery and trauma and have in many of these circumstances have become the standard of care. LMWHs are being use to bridge chronically anti-coagulated patients pre-operatively to surgery on an out patient basis. Further LMWHs are becoming the treatment of choice in acute coronary syndrome and my soon replace unfractonated heparin in this circumstance. LMWHs are therefore a reality of present day medicine and must be integrated into our anesthetic practice. It is therefore imperative anesthesiologist understand these drugs individually and are fluent in the published drug specific guidelines. From this understanding anesthesiologists should participate in the establishment of institutional guidelines so that complications are avoided and outcome optimized.

**References**

Author Information

Dominick Cannavo, MD
Hospital for Joint Diseases

Richard J. Friedman, MD, FRCS[C]
Charleston Orthopedic Associates