Regional Anesthesia in the Anticoagulated Patient: Defining the Risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation)

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Neuraxial anesthesia and analgesia provide several advantages over systemic opioids, including superior analgesia, reduced blood loss and need for transfusion, decreased incidence of graft occlusion, and improved joint mobility following major knee surgery.[1-4] New challenges in the management of patients undergoing neuraxial block have arisen over the last 2 decades, as medical standards for the prevention of perioperative venous thromboembolism were established.[5,6] Concern for patient safety in the presence of potent antithrombotic drugs has resulted in avoidance of regional anesthesia. Indeed, perioperative anesthesia and analgesia are often determined by the antithrombotic agent.[7] Conversely, although the anesthesia community is well aware of the potential for spinal bleeding, other specialties have only recently become cognizant of the risk, as documented by case reports published in the cardiology and neurology literature.[8,9]

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In response to these patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Second Consensus Conference on Neuraxial Anesthesia and Anticoagulation. Portions of the material presented here were published as the proceedings of the 1998 ASRA Consensus Conference.[10-14] The information has been updated to incorporate additional data available since the time of its publication. It is important to note that although the consensus statements are based on a thorough evaluation of the available information, in some cases data are sparse. Numerous studies have documented the safety of neuraxial anesthesia and analgesia in the anticoagulated patient. Unfortunately, with a complication as rare as spinal hematoma, no clinical study to date has sufficient power to definitively determine patient management. Consequently, the pharmacology of hemostasis-altering drugs and case reports of spinal hematoma are also essential to regional anesthetic management. Variances from recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. The consensus statements are designed to encourage safe and quality patient care, but cannot guarantee a specific outcome. They are also subject to timely revision as justified by evolution of information and practice. Finally, the current information focuses on neuraxial blocks and anticoagulants; the risk following plexus and peripheral techniques remains undefined. Although several case reports of vascular injury with (or without) resultant nerve dysfunction have been described,[15,16] additional experience is needed to allow statements for non-neuraxial blocks. The current literature involving hemorrhagic complications of plexus and peripheral block is included for completeness.

Table 1. Pharmacological Venous Thromboembolism Prophylaxis and Treatment Regimens and Treatment Regimens for Acute Coronary Syndromes

Total Hip or Knee Replacement Thromboprophylaxis	
Adjusted-dose unfractionated heparin	3,500 U SC q 8 hours, started 2 hours before surgery; after surgery, the dose is adjusted to maintain the aPTT within the upper normal range
Low molecular weight heparin	
Ardeparin sodium (Normiflow®)	50 U/kg SC q 12 h, started 12-24 hours after surgery
Dalteparin sodium (Fragmin®)	5,000 U SC qd, started 12 hours before surgery, or 2,500 U SC given 7 hours after surgery, then 5,000 U SC daily
Danaparoid sodium (Orgaran®)	750 U SC q 12 h, started 2 hours before surgery
Enoxaparin sodium (Lovenox®)	30 mg SC q 12 h, started 12-24 hours after surgery, or 40 mg SC qd, started 10-12 hours before surgery
Tinzaparin (Innohep®)	75 U/kg SC qd, started 10-12 hours before surgery
Warfarin sodium	5 mg orally, started the night before or immediately after surgery and adjusted to prolong the INR = 2.0-3.0
General Surgery Thromboprophylaxis	
Unfractionated heparin	5,000 U SC q 8-12 hours, started 2 hours before surgery
Low molecular weight heparin	
Dalteparin sodium	2,500 U SC qd, started 1-2 hours before surgery
Enoxaparin sodium	40 mg SC qd, started 2 hours before surgery
Acute Coronary Syndrome and Venous Thromboembolism Therapy	
Enoxaparin sodium	1 mg/kg SC q12 hours (outpatient DVT or non q-wave MI) 1 mg/kg SC q12 hours, or 1.5 mg/kg SC qd (inpatient treatment of DVT or PE)
Dalteparin	120 U/kg q 12 hours or 200 U/kg qd (non q-wave MI)
Tinzaparin	175 U/kg qd

NOTE. Dosing recommendations from Beerts et al.[6]
Abbreviations: SC, subcutaneous; MI, myocardial infarction; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

Current Recommendations for the Prevention and Treatment of Venous Thromboembolism

Thromboprophylaxis is based upon identification of risk factors. Guidelines for antithrombotic therapy including appropriate pharmacologic agent, degree of anticoagulation desired, and duration of therapy continue to evolve.[5,6] Recommendations from the Sixth American College of Chest Physicians (ACCP) Consensus Conference in 2001 are based upon prospective randomized studies that assess the efficacy of therapy using contrast venography or fibrinogen leg scanning to diagnose asymptomatic thrombi (Table 1). Clinical outcomes, such as fatal pulmonary embolism (PE) and symptomatic deep venous thrombosis (DVT) are not primary endpoints.[17] Despite the successful reduction of asymptomatic thromboembolic events with routine use of antithrombotic therapy, an actual reduction of clinically relevant events has been more difficult to demonstrate.[18,19] This is in contrast to the documented improvement in perioperative outcomes in selected patient populations that undergo neuraxial anesthesia and analgesia.[1-4] Thus, establishment of overall risks and benefits of antithrombotic therapy in the patient undergoing neuraxial block is difficult.

Compared with thromboprophylaxis, the presence of acute thromboembolism or unstable angina necessitates more aggressive antithrombotic (and potentially thrombolytic) therapy. For example, acute DVT/PE is treated with therapeutic anticoagulation with unfractionated or low molecular weight heparin (LMWH); thrombolytic therapy may also be utilized alone or concomitantly (Table 1). Likewise, the American College of Cardiology and American Heart Association Task Force on Practice Guidelines for the Management of Patients with Acute Myocardial Infarction recommends a combination therapy of (1) aspirin or (2) ticlopidine/clopidogrel for patients with aspirin intolerance, (3) therapeutic anticoagulation with unfractionated heparin or LMWH, and (4) administration of a platelet glycoprotein (GP) IIb/IIIa receptor antagonist. Intravenous (IV) thrombolytic therapy is recommended in patients with acute (less than 6 hours) symptoms.[20] These treatment modalities have a dramatic impact on the patient's ability to maintain hemostasis. Major bleeding complications may occur spontaneously or at the site of previous trauma, such as vascular access, surgery, or regional block.

Risk of Bleeding Associated With Antithrombotic and Thrombolytic Therapy

Bleeding is the major complication of anticoagulant and thrombolytic therapy. Bleeding is typically

Table 2. Neurologic Outcome in Patients With Spinal Hematoma Following Neuraxial Block

Interval Between Onset of Paraplegia and Surgery	Good N = 15	Partial N = 11	Poor N = 29
Less than 8 hours (N = 13)	6	4	3
Between 8 and 24 hours (N = 7)	1	2	4
Greater than 24 hours (N = 12)	2	0	10
No surgical intervention (N = 13)	4	1	8
Unknown (N = 10)	2	4	4

NOTE. Neurologic outcome was reported for 55 of 61 cases of spinal hematoma following neuraxial block.
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classified as major if it is intracranial, intraspinal, intraocular, mediastinal or retroperitoneal, leads directly to death, or results in hospitalization or transfusion. Risk factors for major bleeding during anticoagulation include the intensity of the anticoagulant effect, increased age, female gender, history of gastrointestinal bleeding, concomitant aspirin use, and length of therapy.[21] During warfarin therapy, an international normalized ratio (INR) of 2.0 to 3.0 is associated with a low risk of bleeding: $< 3\%$ during a 3-month treatment period. Higher intensity regimens (INR > 4) are associated with a significantly greater risk of bleeding (7%). The incidence of hemorrhagic complications during therapeutic anticoagulation with IV or subcutaneous (SC) heparin, as well as LMWH is $< 3\%$.[21] Thrombolytic therapy represents the greatest risk of bleeding; between 6% and 30% of patients were treated with thrombolytic therapy for DVT.[22] Therefore, although thromboembolism remains a source of significant perioperative morbidity and mortality, its prevention and treatment are also associated with risk.

Incidence, Risk Factors, and Neurologic Outcome of Spinal Hematoma

Spinal hematoma, defined as symptomatic bleeding within the spinal neuraxis, is a rare and potentially catastrophic complication of spinal or epidural anesthesia. The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with central neural block is unknown. In an extensive review of the literature, Tryba[23] identified 13 cases of spinal hematoma following 850,000 epidural anesthetics and 7 cases among 650,000 spinal techniques. Based on these observations, the calculated incidence is approximated to be less than 1 in 150,000 epidurals and less than 1 in 220,000 spinal anesthetics.[23] Because these estimates represent the upper limit of the 95% confidence interval, the actual frequency may be much less. Hemorrhage into the spinal canal most commonly occurs in the epidural space, most likely because of the prominent epidural venous plexus, although anesthetic variables, such as needle size and catheter placement, may also affect the site of clinically significant bleeding.[24,25]

In a review of the literature between 1906 and 1994, Vandermeulen et al.[26] reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia. In 42 of the 61 patients (68%), the spinal hematomas associated with central neural block occurred in patients with evidence of hemostatic abnormality. Twenty-five of the patients had received IV or SC (unfractionated or LMWH), while an additional 5 patients were presumably administered heparin as they were undergoing a vascular surgical procedure. In addition, 12 patients had evidence of coagulopathy or thrombocytopenia or were treated with antiplatelet medications (aspirin, indomethacin, ticlopidine), oral anticoagulants (phenprocoumone), thrombolytics (urokinase), or dextran 70 immediately before or after the spinal or epidural anesthetic. Needle and catheter placement was reported to be difficult in 15 (25%), or bloody in 15 (25%) patients. Overall, in 53 of the 61 cases (87%), either a clotting abnormality or needle placement difficulty was present. A spinal anesthetic was performed in 15 patients. The remaining 46 patients received an epidural anesthetic, including 32 patients with an indwelling catheter. In 15 of these 32 patients, the spinal hematoma occurred immediately after the removal of the epidural catheter. Nine of these catheters were removed during therapeutic levels of heparinization. Neurologic compromise presented as progression of sensory or motor block (68% of patients) or bowel/bladder dysfunction (8% of patients), not severe radicular back pain. Importantly, although only 38% of patients had partial or good neurologic recovery, spinal cord ischemia tended to be reversible in patients who underwent laminectomy within 8 hours of onset of neurologic dysfunction[26] (Table 2).

The need for prompt diagnosis and intervention in the event of a spinal hematoma was also demonstrated in a recent review of the American Society of Anesthesiologists (ASA) Closed Claims database, which noted that spinal cord injuries were the

leading cause of claims in the 1990s.[27] Spinal hematomas accounted for nearly half of the spinal cord injuries. Risk factors for spinal hematoma included epidural anesthesia in the presence of IV heparin during a vascular surgical or diagnostic procedure. Importantly, the presence of postoperative numbness or weakness was typically attributed to local anesthetic effect rather than spinal cord ischemia, which delayed the diagnosis. Patient care was rarely judged to have met standards (1 of 13 cases) and the median payment was very high.

Fibrinolytic and Thrombolytic Therapy

Pharmacology of Fibrinolytics/Thrombolytics

The fibrinolytic system dissolves intravascular clots as a result of the action of plasmin. Plasmin is produced by the cleavage of a single peptide bond of the inactive precursor, plasminogen. The resulting compound is a nonspecific protease capable of dissolving fibrin clots and other plasma proteins, including several coagulation factors. Exogenous plasminogen activators, such as streptokinase and urokinase, not only dissolve thrombus, but also affect circulating plasminogen as well. Endogenous t-PA formulations (alteplase and tenecteplase) are more fibrin-selective and have less effect on circulating plasminogen. Clot lysis leads to elevation of fibrin degradation products, which themselves have an anticoagulant effect by inhibiting platelet aggregation. In addition to the fibrinolytic agent, these patients frequently receive IV heparin to maintain an activated partial thromboplastin time (aPTT) of 1.5 to 2 times normal, and often an antiplatelet agent, such as aspirin or clopidogrel. While the plasma half-life of thrombolytic drugs is only hours, it may take days for the thrombolytic effect to resolve; fibrinogen and plasminogen are maximally depressed at 5 hours after thrombolytic therapy and remain significantly depressed at 27 hours. The decrease in coagulation factor levels is greater with streptokinase compared with t-PA therapy. However, the frequency of hemorrhagic events is similar.[28] Importantly, original contraindications to thrombolytic therapy included surgery or puncture of noncompressible vessels within 10 days.[28]

Case Reports of Spontaneous and Regional Anesthesia-Related Spinal Hematomas Related to Thrombolytic Therapy

There are no published studies addressing spinal, epidural, or regional anesthesia in the patient receiving fibrinolytic/thrombolytic therapy. However, there is limited information about these settings available in the form of case reports of spinal hematoma. The majority of published reports involve spontaneous spinal or epidural hematomas after thrombolytic therapy.[29-35] To date, there are 5 cases of spinal hematoma involving the concomitant use of neuraxial anesthesia and fibrinolytic/thrombolytic therapy. Four cases appeared in the literature[8,36-38]; 1 additional case was reported through the MedWatch[1] system. An epidural technique had been performed in 3 patients, a continuous spinal anesthetic in 1 patient, and an epidural steroid injection in the remaining patient. In 3 of the cases, the patients presented with lower extremity ischemia, and a neuraxial anesthetic was performed to allow surgical revascularization. However, 2 of the recent spinal hematomas (including the MedWatch case) occurred in patients who underwent a neuraxial technique (epidural anesthesia for lithotripsy, epidural steroid injection[2]) and subsequently complained of myocardial ischemia and were treated with a thrombolytic.[8] The potential for significant spinal bleeding was not appreciated despite recent neuraxial needle placement in these 2 patients.

Anesthetic Management of the Patient Receiving Thrombolytic Therapy

Patients receiving fibrinolytic/thrombolytic medications are at risk of serious hemorrhagic events, particularly those who have undergone an invasive procedure. Consensus statements are based on the profound effect on hemostasis, the use of concomitant heparin and/or antiplatelet agents (which further increase the risk of bleeding), and the potential for spontaneous neuraxial bleeding with these medications.

Advances in fibrinolytic/thrombolytic therapy have been associated with an increased use of these drugs, which will require further increases in vigilance. Ideally, the patient should be queried prior to the thrombolytic therapy for a recent history of lumbar puncture, spinal or epidural anesthesia, or epidural steroid injection to allow appropriate monitoring. Guidelines detailing original contraindica-

[1] The MedWatch program was initiated in 1993. Reporting of serious adverse events by health care professionals and hospitals is voluntary. Confidentiality is maintained. However, manufacturers and distributors of FDA-approved pharmaceuticals have mandatory reporting requirements. The FDA estimates that less than 1% of serious adverse drug reactions are reported (Goldman, 1996).

[2] An 84-year-old male received an uncomplicated epidural steroid injection in the morning. He developed chest pain later that day, was admitted to the hospital, diagnosed with an acute myocardial infarction (MI), and treated with t-PA and heparin. He subsequently developed back pain and paraplegia. MRI demonstrated an epidural hematoma extending from T10 to the sacrum. Treatment and outcome were not reported.

tions for thrombolytic drugs suggest avoidance of these drugs for 10 days following puncture of noncompressible vessels.

Preoperative evaluation should determine whether fibrinolytic or thrombolytic drugs have been used preoperatively or have the likelihood of being used intraoperatively or postoperatively. Patients receiving fibrinolytic and thrombolytic drugs should be cautioned against receiving spinal or epidural anesthetics except in highly unusual circumstances. Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.

In those patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy, neurologic monitoring should be continued for an appropriate interval. It may be that the interval of monitoring should not be more than 2 hours between neurologic checks. Furthermore, if neuraxial blocks have been combined with fibrinolytic and thrombolytic therapy and ongoing epidural catheter infusion, the infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurologic function.

There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. The measurement of fibrinogen level (one of the last clotting factors to recover) may be helpful in making a decision about catheter removal or maintenance.

Unfractionated IV and SC Heparin

Pharmacology of Unfractionated Heparin

The major anticoagulant effect of heparin is due to a unique pentasaccharide that binds to antithrombin (AT) with high affinity and is present in approximately one third of heparin molecules. Binding of this heparin pentasaccharide to AT accelerates its ability to inactivate thrombin (factor IIa), factor Xa, and factor IXa. Anticoagulant activities of unfractionated heparin depend on both the number of heparin molecules with the pentasaccharide chain and the size of the molecules containing the pentasaccharide sequence. Larger molecular weight heparins will catalyze inhibition of both factor IIa and Xa. Smaller molecular weight heparins will catalyze inhibition of only factor Xa.[39] IV injection results in immediate anticoagulant activity, whereas SC injection results in a 1- to 2-hour delay. The anticoagulant effect of heparin is both dose- and molecular size-dependent and is not linear, but increases disproportionately with increasing doses. For example, the biologic half-life of heparin increases from 30 minutes after 25 U/kg IV to 60 minutes with 100 U/kg IV.[39]

The anticoagulant effect of heparin is typically monitored with the aPTT. Adequate therapeutic effect (in patients with venous thromboembolism or unstable angina) is achieved with a prolongation of the aPTT to greater than 1.5 times the baseline value, heparin level of 0.2 to 0.4 U/mL or anti-Xa level of 0.3 to 0.7 U/mL.[40] Administration of small dose (5,000 U) SC heparin for prophylaxis of deep venous thrombosis generally does not prolong the aPTT, and is typically not monitored. It can result in unpredictable (10-fold variability) and therapeutic blood concentrations of heparin in some patients within 2 hours after administration.[41]

Risk Factors for Spinal Hematoma in the Heparinized Patient Undergoing Neuraxial Block

The combination of spinal or epidural needle insertion in the presence of anticoagulation with heparin may be associated with increased risk. Much of our information about this association comes from a report of 342 patients who deliberately received systemic therapeutic heparin after lumbar puncture.[42] Until the routine use of computed tomography (CT) in the 1980s, diagnostic subarachnoid puncture was routinely used to select patients for heparin therapy for acute cerebral ischemia. Ruff and Dougherty[42] reported that 7 of 342 patients treated in this manner developed spinal hematomas. Three factors associated with increased risk were identified: $<$ 60-minute time interval between the administration of heparin and lumbar puncture, traumatic needle placement, and concomitant use of other anticoagulants (aspirin). These risk factors have been verified in subsequent large reviews of case reports of hematomas associated with neuraxial procedures in the presence of unfractionated heparin (Table 3).[25] In addition, the results have been utilized to define safe practice protocols for patients undergoing neuraxial block during systemic heparinization, particularly during vascular surgery.[26,43]

Intraoperative Systemic Heparinization

Intraoperative heparinization typically involves IV injection of 5 to 10,000 U heparin during the operative period, particularly in the setting of vascular surgery to prevent coagulation during cross-clamping of arterial vessels.[39] Neuraxial anesthetic techniques are often attractive for these patients, as these techniques may provide reduced morbidity and improved postoperative analgesia.[1] However, the use of neuraxial procedures in the presence of

Table 3. Risk Factors and Estimated Incidence for Spinal Hematoma and Central Neuraxial Anesthesia

	Relative Risk of Spinal Hematoma	Estimated Incidence for Epidural Anesthesia	Estimated Incidence for Spinal Anesthesia
No heparin			
Atraumatic	1.00	1:220,000	1:320,000
Traumatic	11.2	1:20,000	1:29,000
With aspirin	2.54	1:150,000	1:220,000
Heparin anticoagulation following neuraxial procedure			
Atraumatic	3.16	1:70,000	1:100,000
Traumatic	112	1:2,000	1:2,900
Heparin $>$ 1 hr after puncture	2.18	1:100,000	1:150,000
Heparin $<$ 1 hr after puncture	25.2	1:8,700	1:13,000
With aspirin	26	1:8,500	1:12,000

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unfractionated heparin may be associated with an increased risk of epidural hematoma.[26,27]

Most published case series used similar guidelines for patient management, including exclusion of high-risk patients (preexisting coagulopathy) and performance of neuraxial procedure at least 1 hour prior to administration of heparin.[13] The question of how to manage the situation of a bloody or traumatic neuraxial procedure has been raised. Previous case reports suggest that presence of a bloody tap or a traumatic regional block is an associated factor in approximately 50% of spinal hematomas.[26] Although some investigators have recommended cancellation of the surgical procedures should these events occur,[43] there are no clinical data to support this recommendation.[44,45] Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is warranted.

Heparinization may be continued into the postoperative period. Prolonged IV heparin administration is usually performed with a constant IV infusion of heparin, usually with a goal of aPTT prolongation to 1.5 to 2 times the baseline level. The risk of any (spontaneous, surgical, or anesthesia-related) bleeding due to heparin in such an anticoagulated patient may be increased.[21] Most importantly, the initiation of systemic therapeutic heparin therapy for medical or surgical indications in the presence of a neuraxial catheter potentially increases the risk of hematoma formation during catheter removal. In the series by Vandermeulen et al.,[26] half of the spinal hematomas associated with systemic heparinization occurred at the time of catheter removal. In all patients who have undergone systemic heparinization, the heparin should be discontinued for 2 to 4 hours prior to neuraxial catheter removal, coagulation status assessed before manipulation of the catheter, and careful assessment of the presence of sensory and motor function in the lower extremities for at least 12 hours following the catheter removal.

Overall, large published series and extensive clinical experience suggests the use of regional techniques during systemic heparinization does not appear to represent a significant risk.[13] However, the recent reports of paralysis relating to spinal hematoma in the ASA Closed Claims database suggests that these events may not be as rare as suspected and that vigilance is necessary to diagnose and intervene as early as possible, should spinal hematoma be suspected.[27]

Complete Anticoagulation during Cardiopulmonary Bypass

Since the publication of the ASRA Consensus Conference guidelines in 1998,[13] there have been continued discussions regarding the relative risk (and benefit) of neuraxial anesthesia and analgesia in the patient undergoing heparinization for cardiopulmonary bypass. To date, there are no cases of spinal hematoma associated with this technique published or within the Closed Claims Project.[27] A review has recommended certain precautions to be taken[46]: (1) neuraxial blocks should be avoided in a patient with known coagulopathy from any cause; (2) surgery should be delayed 24 hours in the event of a traumatic tap; (3) time from instrumentation to systemic heparinization should exceed 60 minutes; (4) heparin effect and reversal should be tightly controlled (smallest amount of heparin for the shortest duration compatible with therapeutic objectives); and (5) epidural catheters should be removed when normal coagulation is restored, and patients should be closely monitored postoperatively for signs and symptoms of hematoma formation.

These recommendations have been used by most of the published case series, as well as the practice of inserting epidural catheters 24 hours in advance of surgery. Validity of these and future recommendations will need to be determined as experience with neuraxial procedures in these patients increases. In

a recent survey of the membership of the Society of Cardiovascular Anesthesiologists, Goldstein et al.[47] surveyed 3,974 cardiac anesthesiologists and found 7% of their responders used spinal or epidural techniques for cardiac surgery. Interestingly, the majority of anesthesiologists would proceed if frank blood were noted in the spinal or epidural needle.

At the time of the original consensus conference, there were not felt to be enough available data to identify the specific risk associated with this technique.[13,46] Since that time, further reports of small series have appeared, again with no reported complications. Two of these series are retrospective reviews of pediatric cardiac surgery including a total of 250 patients that report no spinal hematomas.[48,49] In these pediatric patients the blocks were performed after induction of general anesthesia prior to surgery 1 hour before full systemic heparinization. In contrast, the adult experience with coronary bypass surgery has continued to follow the practice of placement of the epidural catheters on the evening prior to surgery. Sanchez and Nygard[50] report a large prospective series of 558 patients without complications. Despite the absence of serious sequelae, the debate continues as to the risk-benefit advantages of this technique.[51,52] Recently, the efficacy has been examined in the newer "off-pump" approach to cardiac surgery.[53,54] In a series of 50 patients, Priestly et al.[55] reported improved postoperative analgesia and earlier extubation. However, there was no difference in time to hospital dismissal.[55] Although there were no spinal hematomas, the authors observe that "the use of thoracic epidural analgesia during coronary artery bypass grafting is controversial because the anticoagulation required during surgery raises the concern of increasing the rare but serious risk of permanent spinal cord damage from an epidural hematoma. Such a risk must be balanced by important clinical advantages if the technique is to be justified." Despite improved analgesia, they note that "convincing respiratory, cardiac, or other organ outcome data are lacking."

Another approach to this dilemma is presented by Ho et al. who calculated the risk of hematoma. In a complex mathematical analysis of the probability of predicting a rare event that has not occurred yet, they estimate the probability of a spinal hematoma (based on the totals of 4,583 epidural and 10,840 spinal anesthetics reported without complications) to be in the neighborhood of 1:1,528 for epidural and 1:3,610 for spinal technique.[56] The authors hypothesized that this may be an acceptable risk compared with the mortality of postoperative myocardial infarction in this high-risk population, but concede that the actual risk of hematoma may be higher with broader usage, and that further studies are certainly needed. It is of interest that most authors recognize the risks associated with the immediate perioperative period and are placing indwelling catheters the night before surgery. This may become an increasingly difficult aspect of a practice when the majority of cardiac patients are now also being treated as "morning admission" patients in most hospitals. The future of neuraxial anesthesia and analgesia for coronary bypass surgery remains somewhat unclear.[57]

Low-Dose SC Heparin

Low-dose heparin is commonly used for prophylaxis against development of venous thromboembolism in general and urologic surgery.[58] SC administration of 5,000 U heparin every 12 hours has been used extensively and effectively for prophylaxis against deep venous thrombosis. There is often no detectable change in the clotting parameters, as measured by the aPTT. There are a minority of patients, perhaps up to 15%, who may develop measurable changes in coagulation, although the aPTT rarely exceeds 1.5 times the normal level.[41] There is a smaller subset (2% to 4%) of patients who may become therapeutically anticoagulated during SC heparin therapy. With therapy greater than 5 days, there is a subset of patients who will develop a decrease in the platelet count.[39]

The widespread use of SC heparin and paucity of complications suggest that there is little risk of spinal hematoma associated with this therapy. There are 9 published series totaling over 9,000 patients who have received this therapy without complications,[13] as well as extensive experience in both Europe and United States without a significant frequency of complications. Three surveys of opinions among anesthesiologists in Denmark,[59] Great Britain, and Scotland,[60] and New Zealand[61] report that the majority of anesthesiologists appear to feel that the presence of SC heparin prophylaxis is not a strong contraindication to the performance of neuraxial anesthesia. There are only 4 case reports of neuraxial hematomas, 3 epidural[26] and 1 subarachnoid,[62] during neuraxial block with the use of SC heparin.

Performance of neuraxial block before the injection of SC heparin may be preferable, but there does not appear to be an increased risk with neuraxial block in the presence of SC heparin. Previous investigators have recommended delaying performance of neuraxial blocks for 2 hours after administration of SC heparin.[44] However, this may actually coincide with peak effect, and clinical experience questions the need for this delay.

Since the time of our first consensus conference, one additional spinal hematoma has been reported following epidural catheter placement in a patient receiving SC heparin.[63] The patient had several other risk factors involved, and guidelines for insertion and removal of catheters presented in the previous consensus publication[13] were not followed. Nevertheless, this confirms that there is a small but very limited risk associated with the use of epidural and spinal anesthesia in the presence of SC heparin treatment.

Other areas of heparin therapy have not appeared to increase the incidence of spinal hematoma, at least based upon the case reports in the literature and reports to the MedWatch system. Based on this apparent frequency, there does not appear to be any reason to significantly modify the initial consensus statements.

Anesthetic Management of the Patient Receiving Unfractionated Heparin

Anesthetic management of the heparinized patient was established over 2 decades ago. Initial recommendations have been supported by in-depth reviews of case series, case reports of spinal hematoma, and the ASA Closed Claims Project.

During SC (mini-dose) prophylaxis, there is no contraindication to the use of 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. Because heparin-induced thrombocytopenia may occur during heparin administration, patients receiving heparin for greater than 4 days should have a platelet count assessed prior to neuraxial block and catheter removal.

Combining neuraxial techniques with intraoperative anticoagulation with heparin during vascular surgery seems acceptable with the following cautions: (1) avoid the technique in patients with other coagulopathies; (2) heparin administration should be delayed for 1 hour after needle placement; (3) indwelling neuraxial catheters should be removed 2 to 4 hours after the last heparin dose and the patient's coagulation status is evaluated and reheparinization should occur 1 hour after catheter removal; (4) monitor the patient postoperatively to provide early detection of motor block and consider use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma; (5) although the occurrence of a bloody or difficult neuraxial needle placement may increase risk, there are no data to support mandatory cancellation of a case. Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is warranted.

Currently, insufficient data and experience are available to determine if the risk of neuraxial hematoma is increased when combining neuraxial techniques with the full anticoagulation of cardiac surgery. Postoperative monitoring of neurologic function and selection of neuraxial solutions that minimize sensory and motor block is recommended to facilitate detection of new/progressive neurodeficits.

The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving standard heparin. These medications include antiplatelet medications, LMWH, and oral anticoagulants.

LMWH

Pharmacology, Monitoring, and Reversal of the Anticoagulant Effect of LMWH

The biochemical and pharmacologic properties of LMWH differ from those of unfractionated heparin.[64-67] Most relevant are the lack of monitoring of the anticoagulant response (anti-Xa level), prolonged half-life, and irreversibility with protamine. Prolonged LMWH therapy may be associated with an accumulation of anti-Xa activity and fibrinolysis.[68] In addition, the plasma half-life of LMWH increases in patients with renal failure.[64] LMWHs vary both biochemically and pharmacologically, including molecular weight, anti-IIa and anti-Xa activities, and plasma half-life. However, because there are no adequate trials comparing the efficacy and safety of one LMWH to another, it is impossible to recommend one specific LMWH over another. Experience in Europe suggests that the rate of spinal hematoma is similar among LMWH preparations.[69]

Spinal and Epidural Anesthesia in the Patient Receiving LMWH

The relative rarity of spinal hematoma, as well as the publication of several large studies reported over the last 2 decades, increased the clinician's confidence in management of the anticoagulated patient undergoing neuraxial block. However, a new challenge occurred with the release of LMWH for general use in the United States in May 1993. The pharmacologic differences between LMWH and standard heparin were underestimated; over 40 spinal hematomas were reported through the MedWatch system over a 5-year period. This experience contrasted dramatically with that of European cli-

nicians who had reported only 13 spinal hematomas in patients receiving LMWH despite a decade of extensive clinical use.[14] The marked increase in the frequency of spinal hematoma in patients anticoagulated with LMWH prompted a reevaluation of the relative risks and benefits of neuraxial block.

LMWH Thromboprophylaxis in Europe

The administration of LMWH in patients undergoing spinal or epidural anesthesia was examined by Bergqvist et al.[70,71] in 2 reviews published in 1992 and 1993. These studies represent the European experience with LMWH thromboprophylaxis, since no LMWH preparation had been approved for general use in the United States at that time. Bergqvist et al.[72] identified 19 articles involving 9,013 patients who safely received the combination of LMWH and spinal or epidural anesthesia. Importantly, only 1 case of spinal hematoma had been reported.[72] To further document the safety of LMWH in combination with neuraxial block, the authors noted that although only 9,013 patients were identified in their review, pharmaceutical companies had estimated that several million patients had received LMWH while undergoing neuraxial techniques. Based on these data, Bergqvist et al.[71] concluded that neurologic complications after spinal or epidural anesthesia in patients receiving LMWH thromboprophylaxis are extremely rare, and the combination appeared safe. However, a careful analysis of European literature between the years 1993 and 1995 reveals that consistent practice guidelines among the European societies had been established.[73,74] The recommendations established time intervals between LMWH dosing and needle placement/catheter removal, as well as guidelines for neurologic monitoring.[75] These guidelines were apparently effective in reducing the frequency of spinal hematoma in patients receiving the combination of regional anesthesia and LMWH; only 13 spinal hematomas were reported among the European community between 1989 and 1998.[14] In addition, epidural analgesia is not considered a contraindication to concomitant LMWH thromboprophylaxis in Europe.[76,77] It should be noted that European dosing of LMWH is once daily, with the first dose administered 10 to 12 hours preoperatively.

LMWH Thromboprophylaxis in North America

Enoxaparin (Aventis Pharmaceuticals Products, Inc., Bridgewater, NJ), the first LMWH to be approved by the Food and Drug Administration (FDA) in the United States, was distributed for general use in May 1993. At that time, labeled indications included thromboprophylaxis after major joint replacement. Approved dose scheduling was 30 mg every 12 hours, with the first dose administered as soon as possible after surgery. Within 1 year, 2 cases of spinal hematoma had been voluntarily reported through the MedWatch system. The WARNINGS section of the drug label was revised in March 1995 to caution practitioners of the risk of spinal hematoma in patients with indwelling catheters or concomitant treatment with antiplatelet medications, and the prescribing information was changed to recommend that the first dose be given 12 to 24 hours after surgery (rather than immediately postoperatively).

Despite repeated efforts at relabeling and education, cases of spinal hematoma continued to occur. An FDA Health Advisory was issued in December 1997. In addition, the manufacturers of all LMWH and heparinoids were requested to include a black "boxed warning," a designation used by the FDA to denote adverse events, particularly those that may lead to death or serious injury (Code of Federal Regulations, last updated July 15, 2001), in the labeling of their respective products.

Risk Factors for Spinal Hematoma

A review and update of the LMWH literature was performed in 1997 to determine the incidence and risk factors associated with spinal hematoma, as well as practice differences between Europe and North America.[78] Thirty-nine studies involving 15,151 neuraxial anesthetics performed in combination with perioperative LMWH thromboprophylaxis were identified. Although it was documented that a single dose spinal was performed in nearly half of the patients included, it was impossible to determine the actual number of continuous epidural anesthetics (and the duration of postoperative analgesia) because the anesthetic technique was often recorded as "spinal or epidural" or "regional anesthesia." It is notable that none of the 30 cases of spinal hematoma had occurred within this series.

At the time of the Consensus Conference on Neuraxial Anesthesia and Anticoagulation in April 1998, there were 45 cases of spinal hematoma associated with LMWH, 40 of which involved a neuraxial anesthetic. Severe radicular back pain was not the presenting symptom; most patients complained of new onset numbness, weakness, or bowel and bladder dysfunction. Approximately half of patients undergoing a continuous technique reported neurologic deficits 12 hours or more following catheter removal. Median time interval between initiation of LMWH therapy and neurologic dysfunction was 3 days, while median time to onset

Table 4. Patient, Anesthetic, and LMWH Dosing Variables Associated With Spinal Hematoma

Patient factors
Female gender
Increased age
Anesthetic factors
Traumatic needle/catheter placement
Epidural (compared to spinal) technique
Indwelling epidural catheter during LMWH administration
LMWH dosing factors
Immediate preoperative (or intraoperative) LMWH administration
Early postoperative LMWH administration
Concomitant antiplatelet or anticoagulant medications
Twice daily LMWH administration

of symptoms and laminectomy was over 24 hours. Less than one third of the patients reported fair or good neurologic recovery.[14]

The risk of spinal hematoma (based on LMWH sales, prevalence of neuraxial techniques, and reported cases) was estimated to be approximately 1 in 3,000 continuous epidural anesthetics compared with 1 in 40,000 spinal anesthetics.[79] However, this is most likely an underestimation. In addition to the spinal hematomas that had been reported at the time of the First Consensus Conference, there were approximately 20 more that had occurred, but were not yet reported to the MedWatch system. In total, nearly 60 spinal hematomas were tallied by the FDA between 1993 and 1998.

Based on an examination of the published cases, MedWatch reports, and clinical experience in Europe and North America, specific risk factors have been proposed. It is not possible to stratify the individual risk factors or determine interactions between risk factors (Table 4). A recent clinical investigation has reported a significant anticoagulant effect present at the time of epidural catheter removal in patients receiving twice daily LMWH compared with once daily LMWH administration.[80]

Reports of Spinal Hematoma Since 1998

Since 1998, there have been 6 cases of spontaneous spinal hematomas associated with LMWH, including 1 patient who also received a thrombolytic. These cases represent the newer applications of LMWH, which involve treatment of DVT/PE and acute coronary syndrome (Table 1).

There have been only 13 cases of spinal hematoma following neuraxial block since 1998 reported through the MedWatch system or published as case reports.[81,82] Five cases were from outside the United States, including the 2 published case reports. In addition to LMWH, 5 patients received ketorolac, 1 patient received ibuprofen,[82] and 1 patient received IV unfractionated heparin during a vascular procedure. The regional technique was a spinal anesthetic in 3 cases. The remaining 10 patients underwent epidural anesthesia in combination with LWMH therapy. Thus, the characteristics of the reported cases support the previous recommendations of epidural catheter removal prior to the initiation of LMWH thromboprophylaxis and avoidance of concomitant antiplatelet/anticoagulant medications. Although the number of cases voluntarily reported has markedly declined, this may be a result of decreased reporting, improved management, or simple avoidance of all neuraxial techniques in patients receiving LMWH. Continued monitoring is necessary.

New Applications of LMWH

The indications and labeled uses for LMWH continue to evolve. Indications for thromboprophylaxis as well as treatment of DVT/PE or MI have been introduced since the first Consensus Conference. These new applications and corresponding regional anesthetic management warrant discussion. Additional research has been performed regarding the efficacy of a single daily dose of LMWH for thromboprophylaxis following major joint surgery. Previous labeling had included a once daily dose of enoxaparin 40 mg; however, the first dose was administered 12 hours preoperatively. Since this necessitated hospital admission the night before surgery, it was seldom utilized. Rather, the twice-daily dosing regimen of enoxaparin 30 mg every 12 hours, with the first dose administered postoperatively, was most common. Recently, the efficacy of single daily administration, with postoperative initiation of therapy, has been approved for Dalteparin (Pharmacia and Upjohn Company, Kalamazoo, MI).[83] This application involves administration of half the usual dose (2,500 U) approximately 6 to 8 hours postoperatively. The next dose (5,000 U) is given 24 hours later. This regimen approximates the European dosing schedule, but without the preoperative dose. Thus, it should be possible to manage patients according to European guidelines. Indwelling epidural catheters may be safely maintained with this administration. However, timing of both the first and subsequent doses of dalteparin should be confirmed to assure an adequate time interval between LMWH doses as well as needle placement/catheter removal.

Several off-label applications of LMWH are of special interest to the anesthesiologist. LMWH has been demonstrated to be efficacious as a "bridge therapy" for patients chronically anticoagulated with warfarin, including parturients, patients with prosthetic cardiac valves, a history of atrial fibrilla-

tion, or a preexisting hypercoagulable condition.[84] In anticipation of surgery, warfarin is discontinued and the prothrombin time allowed to normalize. During this time, the patient would be at risk for thromboembolic events, and historically would be hospitalized and heparinized systemically. Outpatient LMWH is a suitable alternative. The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher (Table 1). Needle placement should occur a minimum of 24 hours following this level of LMWH anticoagulation. It is also important to determine when the first postoperative dose is anticipated, because these patients are often aggressively anticoagulated postoperatively. In these cases, a spinal or a general anesthetic may be the safest alternatives.

Efficacy of Management Guidelines in Reducing the Risk of Spinal Hematoma

Perioperative management of patients receiving LMWH requires coordination and communication. Time intervals between neuraxial needle placement and administration of LMWH must be maintained. However, hospital staffs often administer LMWH at a set time (usually 7 to 8 AM and 7 to 8 PM), unless otherwise specified. It is also important to note that even when protocols for dosing of LMWH and catheter management exist, they may not be closely followed. McEvoy et al.[85] reported a 52% noncompliance rate in the administration of LMWH in association with epidural analgesia. Clinicians are urged to develop protocols that "fit" within the normal practice standards at their institutions rather than deviate from the routine.

Anesthetic Management of the Patient Receiving LMWH

Anesthesiologists in North America can draw on the extensive European experience to develop practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. All consensus statements contained herein respect the labeled dosing regimens of LMWH as established by the FDA. Although it is impossible to devise recommendations that will completely eliminate the risk of spinal hematoma, previous consensus recommendations have appeared to improve outcome. Concern remains for higher dose applications, where sustained therapeutic levels of anticoagulation are present.

Monitoring of the anti-Xa level is not recommended. The anti-Xa level is not predictive of the risk of bleeding and is, therefore, not helpful in the management of patients undergoing neuraxial blocks.

Antiplatelet or oral anticoagulant medications administered in combination with LMWH may increase the risk of spinal hematoma. Concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, represents an additional risk of hemorrhagic complications perioperatively, including spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects.

The presence of blood during needle and catheter placement does not necessitate postponement of surgery. However, initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively. Traumatic needle or catheter placement may signify an increased risk of spinal hematoma, and it is recommended that this consideration be discussed with the surgeon.

Preoperative LMWH

Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, needle placement should occur at least 10 to 12 hours after the LMWH dose.

Patients receiving higher (treatment) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily will require delays of at least 24 hours to assure normal hemostasis at the time of needle insertion.

Neuraxial techniques should be avoided in patients administered a dose of LMWH 2 hours preoperatively (general surgery patients), because needle placement would occur during peak anticoagulant activity.

Postoperative LMWH

Patients with postoperative initiation of LMWH thromboprophylaxis 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.

Twice Daily Dosing. This dosage regimen may be associated with an increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hours postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed prior to initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight and removed the following day, with the first dose of LMWH administered 2 hours after catheter removal.

Single Daily Dosing. This dosing regimen approximates the European application. The first postoperative LMWH dose should be administered 6 to 8 hours postoperatively. The second postoperative dose should occur no sooner than 24 hours after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10 to 12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hours after catheter removal.

Oral Anticoagulants (Warfarin)

Warfarin Pharmacology

Oral anticoagulants, including warfarin, exert their anticoagulant effect indirectly by interfering with the synthesis of the vitamin K-dependent clotting factors, factor II (thrombin), VII, IX, and X. The effects of warfarin are not apparent until a significant amount of biologically inactive factors are synthesized and is dependent on factor half-life[86]: factor VII, 6 to 8 hours; factor IX, 24 hours; factor X, 25 to 60 hours; and factor II, 50 to 80 hours.

An understanding of the correlation between the various vitamin K–dependent factor levels and the INR is critical to regional anesthetic management. Clinical experience with patients who congenitally are deficient in factors II, IX, or X suggests that a factor activity level of 40% for each factor is adequate for normal or near-normal hemostasis.[87] Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. The PT and INR are most sensitive to the activities of factors VII and X and are relatively insensitive to factor II.[88] Because factor VII has a relatively short half-life, prolongation of the PT and INR may occur in 24 to 36 hours. Prolongation of the INR (INR $>$ 1.2) occurs when factor VII activity is reduced to approximately 55% of baseline, while an INR = 1.5 is associated with a factor VII activity of 40%.[86] Thus, an INR $<$1.5 should be associated with normal hemostasis.

The same principles apply during recovery of normal hemostasis upon discontinuation of warfarin therapy. Factor VII activity will rapidly increase, as demonstrated by a decrease in the INR. However, factor II and X activities recover much more slowly; hemostasis may not be adequate even though the INR is 1.4 or less.[88] Adequate levels of all vitamin K-dependent factors are typically present when the INR is in the normal range. In emergent situations, the effects of warfarin may be reversed by injection of vitamin K and/or transfusion of fresh frozen plasma.[88]

Factors Affecting Warfarin Response

The measured response to anticoagulant therapy at the initiation of treatment varies significantly. Some of the variability may be attributed to drug interactions, but in addition there are patient variables, such as age, female gender, and preexisting medical conditions (lower patient weight, liver, cardiac, and renal disease) that are associated with an enhanced response to warfarin.[89,90] Oriental patients require lower doses than Caucasian patients during chronic therapy.[89] In addition, there are many drug interactions described with warfarin therapy that potentiate the anticoagulant effect, including concomitant administration of antiplatelet medications, heparin, and LMWH.[91,92]

Warfarin is a drug with a narrow therapeutic range. Attention to the individual patient's response to warfarin therapy and maintenance of a consistent level of anticoagulation is paramount. Most medical laboratories have a method of contacting the caregiver in the event of an excessively prolonged PT/INR. However, further precautions may be warranted. Inclusion of pharmacy personnel may be one technique to add consistency in warfarin management. Because all warfarin orders are filled by the pharmacy (and entered into a central computer), linking the pharmacy and laboratory results' computers will allow identification of patients with (1) a significant increase in the INR in a predefined time, (2) a subtherapuetic INR, and (3) warfarin therapy without INR assessment. The pharmacy then notifies the primary service and/or pain service so that appropriate action may be taken. To maintain the desired anticoagulant effect, the patient is instructed in a "warfarin" diet that contains foods with a consistent (low) level of vitamin K. These procedures have been successfully implemented at the Mayo Clinic.

Neuraxial Techniques in the Chronically Anticoagulated Patient

Although no studies have directly examined the risk of procedure-related bleeding and the INR in patients recently discontinued from warfarin, careful consideration should be given before performing neuraxial blocks in these patients. Labeling of warfarin in the United States specifically lists spinal puncture and lumbar block anesthesia as contraindicated during warfarin therapy that is not interrupted prior to surgery.[93] Wille-Jorgensen et al.[90] reported a case of difficult epidural placement in a patient fully anticoagulated with phenprocoumon. The anticoagulant therapy was unknown to the anesthesiologist. There was no bleeding observed during catheter placement, although placement was technically difficult. Satisfac-

tory anesthesia developed and apparently resolved. Three days after surgery, the patient developed paresis of the lower extremities and impairment of the rectal and bladder sphincters. An epidural hematoma was evacuated from T11-L1, but the extremity paresis was not reversed.

Timing of Neuraxial Catheter Removal During Warfarin Thromboprophylaxis

The management of patients requiring chronic anticoagulation (with recent discontinuation of warfarin in anticipation of surgery) and patients receiving warfarin perioperatively for thromboprophylaxis remains controversial. Adjusted-dose warfarin is the most common agent used for thromboembolism prophylaxis after hip and knee replacement surgery (Table 1). Few data exist regarding the risk of spinal hematoma in patients with indwelling spinal or epidural catheters who are subsequently anticoagulated with warfarin. Bleeding may occur during catheter removal of the epidural catheter as a result of vascular trauma during catheter manipulation[94] or dislodgment of an existing clot.[95]

Several studies have examined the use of regional anesthesia and analgesia in patients who received warfarin during the perioperative period for thromboembolic prophylaxis. No spinal hematomas were reported in any of the studies; however, the power of these studies to detect a rare complication is low. Odoom and Sih[96] performed 1,000 continuous lumbar epidural anesthetics in 950 patients undergoing vascular procedures who were receiving oral anticoagulants preoperatively. The thrombotest (a test measuring factor IX activity) was decreased and the aPTT was prolonged in all patients prior to needle placement. A modest heparin infusion was administered intraoperatively. Epidural catheters remained in place for 48 hours postoperatively; the coagulation status at time of catheter removal was not described. There were no neurologic complications. While the results of this study are reassuring, the obsolescence of the thrombotest as a measure of anticoagulation combined with the unknown coagulation status of the patients at the time of catheter removal limit their usefulness.

The use of an indwelling epidural or intrathecal catheter and the timing of its removal in an anticoagulated patient are also controversial. Although the trauma of needle placement occurs with both single dose and continuous catheter techniques, the presence of an indwelling catheter could theoretically provoke additional injury to tissue and vascular structures. A combined series of 651 patients reported no spinal hematomas in patients receiving neuraxial block in conjunction with low-dose warfarin therapy. The mean INR at the time of catheter removal was 1.4. However, marked variability in patient response to warfarin was noted.[97,98]

There are 2 case reports in the literature describing spinal hematoma in patients who received perioperative warfarin for thromboembolic prophylaxis and regional anesthesia. Woolson et al.[99] reported an 85-year-old woman who underwent total knee arthroplasty (TKA) with epidural anesthesia and analgesia. The patient was given a single preoperative dose of 10 mg warfarin. Her epidural catheter was removed on the second postoperative day, at which time her INR was 6.3. She developed paraparesis of the lower extremities, which required laminectomy. Badenhorst[100] described a female patient who underwent bilateral TKA with epidural anesthesia and analgesia. This patient also received a preoperative dose of warfarin that was continued throughout the perioperative period. Her PT the morning of surgery was 14.3 seconds (normal, 11.2 to 14.4 seconds; INR not reported). On the third postoperative day, the epidural catheter was removed when her PT was 17.3 seconds. At that time she complained of blurred vision and tingling and weakness in her right leg. On postoperative day 4, she had bilateral lower extremity sensory and motor deficits. She underwent emergent decompressive laminectomy with near complete recovery. Two cases of spinal hematomas in patients anticoagulated with warfarin have been reported through the MedWatch system since 1998. The details are scant for both cases. The first patient was chronically anticoagulated with warfarin with a PT greater than 50 seconds at the time of needle placement. The second patient received epidural analgesia and developed neurologic deficits 48 hours later (with the catheter indwelling), at which time her INR was 1.6. Although a laminectomy was performed, neurologic outcome was not noted.

Regional Anesthetic Management of the Patient on Oral Anticoagulants

The management of patients receiving warfarin perioperatively remains controversial. Consensus statements are based on warfarin pharmacology, the clinical relevance of vitamin K coagulation factor levels/deficiencies, and the case reports of spinal hematoma among these patients.

Caution should be used when performing neuraxial techniques in patients recently discontinued from chronic warfarin therapy. The anticoagulant therapy must be stopped, (ideally 4 to 5 days prior to the planned procedure) and the PT/INR measured prior to initiation of neuraxial block. Early after discontinuation of warfarin therapy, the

PT/INR reflect predominantly factor VII levels, and despite acceptable factor VII levels, factors II and X levels may not be adequate for normal hemostasis. Adequate levels of II, VII, IX, and X may not be present until the PT/INT is within normal limits.

The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving oral anticoagulants, and do so without influencing the PT/INR. These medications include aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), ticlopidine and clopidogrel, unfractionated heparin, and LMWH.

For patients receiving an initial dose of warfarin prior to surgery, the PT/INR should be checked prior to neuraxial block if the first dose was given more than 24 hours earlier or a second dose of oral anticoagulant has been administered.

Patients receiving low-dose warfarin therapy during epidural analgesia should have their PT/INR monitored on a daily basis and checked before catheter removal, if initial doses of warfarin are administered more than 36 hours preoperatively. Initial studies evaluating the safety of epidural analgesia in association with oral anticoagulation utilized mean daily doses of approximately 5 mg warfarin. Higher dose warfarin may require more intensive monitoring of the coagulation status.

As thromboprophylaxis with warfarin is initiated, neuraxial catheters should be removed when the INR is <1.5. This value was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%.

Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. The type of analgesic solution should be tailored to minimize the degree of sensory and motor block. These checks should be continued after catheter removal for at least 24 hours, and longer if the INR was greater than 1.5 at the time of catheter removal.

An INR $>$ 3 should prompt the physician to withhold or reduce the warfarin dose in patients with indwelling neuraxial catheters. We can make no definitive recommendation for removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion.

Reduced doses of warfarin should be given to patients who are likely to have an enhanced response to the drug.

Antiplatelet Medications

Pharmacology of "Antiplatelet" Medications

Antiplatelet agents include NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban). It is important to note the pharmacologic differences among the drugs with antiplatelet effects.

Cyclooxygenase (COX) exists in 2 forms. COX-1 regulates constitutive mechanisms, while COX-2 mediates pain and inflammation. NSAIDs inhibit platelet COX and prevent the synthesis of thromboxane A2. Platelets from patients who have been taking these medications have normal platelet adherence to subendothelium and normal primary hemostatic plug formation. Depending on the dose administered, aspirin (and other NSAIDs) may produce opposing effects on the hemostatic mechanism. For example, platelet COX is inhibited by low-dose aspirin (60 to 325 mg/d) while larger doses (1.5 to 2 g/d) will also inhibit the production of prostacyclin (a potent vasodilator and platelet aggregation inhibitor) by vascular endothelial cells. It has been suggested that the Ivy bleeding time is the most reliable predictor of abnormal bleeding in patients receiving antiplatelet drugs. However, there is no evidence to suggest that a bleeding time can predict hemostatic compromise.[101] Platelet function is affected for the life of the platelet following aspirin ingestion; other nonsteroidal analgesics (naproxen, piroxicam, ibuprofen) produce a short-term defect, which normalizes within 3 days.[102]

Celecoxib (Celebrex, Pfizer, New York, NY) and Rofecoxib (Vioxx, Merck and Co. Inc., Whitehouse Station, NY) are anti-inflammatory agents that primarily inhibit COX-2, an inducible enzyme which is not expressed in platelets, and thus does not cause platelet dysfunction.[103] After single and multidosing, there have not been findings of significant disruption of platelet aggregation, nor is there a history of undesirable bleeding events. The concomitant use of COX-2 inhibitors and warfarin may increase the risk of hemorrhagic complications by increasing the PT.

The antiplatelet effect of the thienopyridine derivatives, ticlopidine and clopidogrel, results from inhibition of adenosine diphosphate (ADP)-induced platelet aggregation. These antiplatelet agents, used in the prevention of cerebrovascular thromboembolic events, affect both primary and secondary platelet aggregation. Ticlopidine (Ticlid, Roche Laboratories, Nutley, NJ) and clopidogrel (Plavix, Bristol-Myers Squibb Co., New York, NY) also interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions.[104] Thienopyridine derivatives demonstrate both time- and dose-dependent effects; steady state is achieved within 7 days for clopidogrel and 14 to 21 days for ticlopidine. Although often administered in combination with

aspirin, the safety of concomitant use of clopidogrel or ticlopidine and aspirin has not been established and may be associated with increased risk of hemorrhagic events. Serious hematologic adverse reactions, including agranulocytosis, thrombotic thrombocytopenic purpura, and aplastic anemia have resulted in placement of a black box warning on ticlopidine. Labeling recommends, "If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, clopidogrel should be discontinued 7 days and ticlopidine 10-14 days, prior to surgery."

Platelet GP IIb/IIIa receptor antagonists, including abciximab (Reopro, Eli Lilly and Co., Indianapolis, IN), eptifibatide (Integrilin, Millenium Pharmaceuticals Inc., San Francisco, CA), and tirofiban (Aggrastat, Merck and Co.), inhibit platelet aggregation by interfering with platelet-fibrinogen and platelet-von Willebrand factor binding. Because fibrinogen and von Willebrand factor have multiple binding sites, they can bind to multiple platelets, causing cross-linking and platelet aggregation. Conversely, inhibition of GP IIb/IIIa receptors blocks the final common pathway to platelet aggregation. The majority of clinical trials involving the GP IIb/IIIa antagonists have evaluated their use in the treatment of acute coronary syndrome (with or without percutaneous coronary intervention). Importantly, the GP IIb/IIIa antagonists are typically administered in combination with aspirin and heparin. Contraindications include a history of surgery within 4 to 6 weeks. Time to normal platelet aggregation following discontinuation of therapy ranges from 8 hours (eptifibatide, tirofiban) to 24 to 48 hours (abciximab). During therapy with GP IIb/IIIa antagonists, labeling precautions recommend that puncture of noncompressible sites and "epidural" procedures be avoided.

Spinal Hematoma in Patients Receiving Antiplatelet Medications

At the 1998 Consensus Conference on Neuraxial Anesthesia and Anticoagulation, it was concluded that NSAIDs, in and of themselves, did not appear to present significant risk to patients for developing spinal-epidural hematomas.[11] Vandermeulen et al.[26] implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia. These patients had received aspirin, indomethacin, or ticlopidine. Three additional case reports related to neuraxial techniques have been published in recent years, 2 involving ketorolac and 2 involving a thienopyridine derivative.[105-108] The paucity of case reports is important, given the prevalence of NSAID use among the general population and that subset of patients with acute, chronic, and/or cancer pain-related problems who subsequently receive interventional therapy.

Several large studies have demonstrated the relative safety of central neural block in combination with antiplatelet therapy, although the total number of patients in this combined series is only 4,714.[11] If low-dose aspirin creates the greatest impact on platelet function, patients receiving 60 to 325 mg aspirin would theoretically represent the greatest risk of significant bleeding. However, the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) Group included 1,422 high-risk obstetric patients administered 60 mg aspirin daily who underwent epidural anesthesia without any neurologic sequelae.[109] A recent prospective study evaluated the risk of neurologic complications following epidural steroid injection. There were no spinal hematomas among the 1,214 patients, including the 32% of patients who reported NSAID use prior to injection.[110] These results confirm those of previous studies performed in obstetric and surgical populations.

No series involving the performance of neuraxial block in the presence of thienopyridine derivatives or platelet GP IIb/IIIa receptor antagonists has been performed. Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel, and GP IIb/IIIa antagonists has been noted.[111,112] In general, the cardiac surgical[112] and interventional radiology literature recommend that elective surgery be delayed 24 to 48 hours following abciximab and 4 to 8 hours following eptifibatide or tirofiban.[113] Surgery performed within 12 hours of abciximab administration will most likely necessitate a platelet transfusion. There have been 3 spinal hematomas attributed to neuraxial techniques and ticlopidine or clopidogrel, including 1 patient undergoing a series of epidural steroid injections.[106,108,114] Two cases of severe bleeding following lumbar sympathetic block in patients on ticlopidine and clopidogrel were recently reported, which may warrant concern regarding the risk of anesthesia-related hemorrhagic complications.[16]

Combination of Antiplatelet Medications With Anticoagulants and Thrombolytics

NSAIDs alone do not significantly increase the risk of spinal hematoma. However, combination therapy with unfractionated heparin, LMWH, oral anticoagulants, and thrombolytics have been demonstrated to increase the frequency of spontaneous hemorrhagic complications, bleeding at puncture

Table 5. Three Herbal Medications With the Greatest Impact on Hemostasis

Herb	Important Effects	Perioperative Concerns	Time to Normal Hemostasis After Discontinuation
Garlic	Inhibition of platelet aggregation (may be irreversible) Increased fibrinolysis Equivocal antihypertensive activity	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginko	Inhibition of platelet-activating factor	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	36 hours
Ginseng	Lowers blood glucose Increased prothrombin and activated partial prothrombin times in animals Other diverse effects	Hypoglycemia Potential to increase risk of bleeding Potential to decrease anticoagulant effect of warfarin	24 hours

NOTE. At this time, it is not deemed necessary to discontinue herbal medications and allow resolution of their effects on hemostasis prior to surgery or anesthesia.

sites, and spinal hematoma.[14,18,22,42] For example, in the series of 40 spinal hematomas associated with LMWH reported in 1998, 10 patients received concomitant antiplatelet medications. Likewise, in a case report of spinal hematoma following epidural steroid injection, Benzon et al.[106] noted the patient had received multiple antiplatelet medications, including clopidogrel and aspirin.

Anesthetic Management of the Patient Receiving Antiplatelet Medications

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) exert diverse effects on platelet function. The pharmacologic differences make it impossible to extrapolate between the groups of drugs regarding the practice of neuraxial techniques.

There is no wholly accepted test, including the bleeding time, which will guide antiplatelet therapy. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. These conditions include a history of easy bruisability/excessive bleeding, female gender, and increased age.

NSAIDs appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that will interfere with the performance of neuraxial blocks.

At this time, there do not seem to be specific concerns as to the timing of single-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal.

The actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown. Consensus management is based on labeling precautions and the surgical, interventional cardiology/radiology experience.

Based on labeling and surgical reviews, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial block is 14 days for ticlopidine and 7 days for clopidogrel.

Platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. Following administration, the time to normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. Although GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery, should one be administered in the postoperative period (following a neuraxial technique), the patient should be carefully monitored neurologically.

The concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, unfractionated heparin, and LMWH, may increase the risk of bleeding complications. COX-2 inhibitors have minimal effect on platelet function and should be considered in patients who require anti-inflammatory therapy in the presence of anticoagulation.

Effects of Herbal Therapies on Coagulation

There is a widespread use of herbal medications in surgical patients. Most patients do not volunteer information regarding herbal medication use; obtaining such a history may be difficult.[115-117] Morbidity and mortality associated with herbal use may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur. Such complications include bleeding from garlic, ginkgo, and ginseng, and potential interaction between ginseng-warfarin (Table 5). Be-

cause the current regulatory mechanism for commercial herbal preparations sold in the United States does not adequately protect against unpredictable or undesirable pharmacological effects, it is especially important for anesthesiologists to be familiar with related literature on herbal medications when caring for patients in the perioperative period. Sources for reliable and updated information are important in helping anesthesiologists stay abreast of new discoveries about the effects of herbal medications in humans. Several resources are available on the World Wide Web as clinical aids. The Center for Food Safety and Applied Nutrition, Food and Drug Administration (http://vm.cfsan.fda.gov/~dms/supplmnt.html) and National Center for Complementary and Alternative Medicine, National Institutes of Health (http://nccam.nih.gov) websites contain fact sheets about alternative therapies, consensus reports, and databases. The FDA website may also be used to report adverse events.

Garlic

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk of developing atherosclerosis by reducing blood pressure, thrombus formation, and serum lipid and cholesterol levels.[118] The usual dosage is 4 g (~2 cloves) of fresh bulb or its equivalent as an extract or tincture per day.[119] Garlic inhibits in vivo platelet aggregation in a dose-dependent fashion. The effect of one of its constituents, ajoene, appears to be irreversible and may potentiate the effect of other platelet inhibitors, such as prostacyclin, forskolin, indomethacin, and dipyridamole.[120,121] Although these effects have not been consistently demonstrated in volunteers, there is 1 case in the literature of an octagenarian who developed a spontaneous epidural hematoma that was attributed to heavy garlic use.[122]

Ginkgo

Ginkgo is derived from the leaf of Ginkgo biloba. It has been used in cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness.[123,124] The compounds believed to be responsible for its pharmacologic effects are the terpenoids and flavonoids. The usual dosage is 120 to 240 mg standardized extract per day in 2 or 3 divided doses.[125] Ginkgo appears to inhibit platelet-activating factor (PAF).[126] Clinical trials in a small number of patients have not demonstrated bleeding complications, but 4 reported cases of spontaneous intracranial bleeding[127-130] have been associated with ginkgo use.

Ginseng

Among the several species used for pharmacologic effects, Asian ginseng and American ginseng are the most commonly described. Ginseng has been labeled an "adaptogen" because it reputedly protects the body against stress and restores homeostasis.[131] The usual dosage is 1 to 2 g root or 200 mg standardized extract per day.[132] Ginseng has a broad, but incomplete, pharmacologic profile, because it has many heterogeneous and sometimes opposing effects of different ginsenosides.[133] There is a concern about ginseng's effect on coagulation pathways. Ginsenosides inhibit platelet aggregation in vitro[134,135] and prolong both thrombin time and activated partial thromboplastin time in rats.[136] These findings await confirmation in humans. Although ginseng may inhibit the coagulation cascade, ginseng use was associated with a significant decrease in warfarin anticoagulation in 1 reported case.[137]

Anesthetic Management of the Patient Receiving Herbal Therapy

Herbal drugs, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. This is an important observation, because it is likely that a significant number of our surgical patients utilize alternative medications preoperatively and perhaps during their postoperative course.

The use of herbal medications alone does not create a level of risk that will interfere with the performance of neuraxial blocks. Mandatory discontinuation of these medications or cancellation of surgery in patients in whom these medications have been continued is not supported by available data.

Data on the combination of herbal therapy with other forms of anticoagulation are lacking. However, the concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants or heparin, may increase the risk of bleeding complications in these patients.

There is no wholly accepted test to assess adequacy of hemostasis in the patient reporting preoperative herbal medications.

At this time, there do not seem to be specific concerns as to the timing of neuraxial block in relationship to the dosing of herbal therapy, postoperative monitoring, or the timing of neuraxial catheter removal.

New Anticoagulants

New antithrombotic drugs, which target various steps in the hemostatic system, such as inhibiting platelet aggregation, blocking coagulation factors, or enhancing fibrinolysis, are continually under development. The most extensively studied are antagonists of specific platelet receptors and direct thrombin inhibitors. Many of these antithrombotic agents have prolonged half-lives and are difficult to reverse without administration of blood components. It is likely that orally bioavailable "heparins" will be introduced in the near future. The administration of these medications in combination with neuraxial anesthesia must be carefully considered.

Thrombin Inhibitors

Recombinant hirudin derivatives, including desirudin (Revasc, Aventis Pharmaceuticals, Paris, France), lepirudin (Refludan, Aventis Pharmaceuticals), and bivalirudin (Angiomax, The Medicine Co., Cambridge, MA) inhibit both free and clot-bound thrombin. Argatroban (Acova), an L-arginine derivative, has a similar mechanism of action. These medications are indicated for the treatment and prevention of thrombosis in patients with heparin-induced thrombocytopenia and as an adjunct to angioplasty procedures.[138,139] Desirudin has also been evaluated for prevention of DVT/PE following hip replacement.[140] The anticoagulant effect of thrombin inhibitors is monitored by the aPTT, and is present for 1 to 3 hours after IV administration. Hemorrhagic complications, particularly when combined with thrombolytic or antiplatelet agents, may be life threatening. There is no "antidote"; the antithrombin effect cannot be reversed pharmacologically. Although there are no case reports of spinal hematoma related to neuraxial anesthesia among patients who have received a thrombin inhibitor, spontaneous intracranial bleeding has been reported. Due to the lack of information available, no statement regarding risk assessment and patient management can be made. Identification of cardiology and surgical risk factors associated with bleeding following invasive procedures may be helpful.

Fondaparinux

Fondaparinux, an injectable synthetic pentasaccharide, was approved in December 2001. The FDA released fondaparinux (Arixtra, Sanofi-Synthelabo, West Orange, NJ) with a black box warning similar to that of the LMWHs and heparinoids. Fondaparinux produces its antithrombotic effect through factor Xa inhibition. The plasma half-life of fondaparinux is 21 hours, allowing for single daily dosing, with the first dose administered 6 hours postoperatively.[141] Investigators reported a spinal hematoma among the initial dose-ranging study (at a dose that was subsequently determined to be twice required for thromboprophylaxis).[142,143] No additional spinal hematomas were reported in the combined series of 3,600 patients who underwent spinal or epidural anesthesia in combination with fondaparinux thromboprophylaxis. However, the conditions for performance of neuraxial block were strictly controlled. Patients were included in subsequent clinical trials only if needle placement was atraumatic and accomplished on the first attempt. In addition, indwelling epidural catheters were removed 2 hours prior to fondaparinux administration.[143] These practice guidelines may not be feasible in clinical practice. For example, in a prospective series, less than 40% of neuraxial blocks were successful with one pass.[24]

Anesthetic Management of the Patient Receiving Fondaparinux

The actual risk of spinal hematoma with fondaparinux is unknown. Consensus statements are based on the sustained and irreversible antithrombotic effect, early postoperative dosing, and the spinal hematoma reported during initial clinical trials. Close monitoring of the surgical literature for risk factors associated with surgical bleeding may be helpful in risk assessment and patient management.

Until further clinical experience is available, performance of neuraxial techniques should occur under conditions utilized in clinical trials (single needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters). If this is not feasible, an alternate method of prophylaxis should be considered.

German and Spanish Guidelines for Thromboembolism Prophylaxis and Regional Anesthesia

Every year, several million neuraxial blocks are performed in Europe, the majority on patients undergoing in-patient surgery who receive thromboembolic prophylaxis, usually with either unfractionated or LMWH. The reported incidence of clinically important spinal bleeding resulting in permanent neurologic lesions is extremely low. It is important to note that 70% to 75% of neuraxial blocks performed in Europe are single-dose spinal anesthetics; continuous epidural techniques account for only 19% of central blocks.[69]

Consensus statements tend to reflect the clinical experience and concerns of the conference partici-

Table 6. Neuraxial Anesthesia in the Patient Receiving Thromboprophylaxis

	Antiplatelet Medications	Unfractionated Heparin		Low Molecular Weight Heparin	Warfarin	Thrombolytics	Herbal Therapy
		Subcutaneous	Intravenous				
German Society of Anesthesiology and Intensive Care Medicine	No contraindication	Needle placement 4 h after heparin; heparin 1 h after needle placement or catheter removal	Needle placement and/or catheter removal 4 h after discontinuing heparin, heparinize 1 h after neuraxial technique; delay surgery 12 h if traumatic	Neuraxial technique 10-12 h after LMWH; next dose 4 h after needle or catheter placement	Discontinue in advance, remove catheter prior to initiation of warfarin	Not discussed	Not discussed
Spanish Consensus Forum	Discontinue in advance	Not discussed	Neuraxial technique 4 h after heparin dose; heparinize 30 min after needle placement; delay heparinization 6 h if traumatic	Needle placement 12+ h after LMWH; first postoperative dose 4-12 h; catheters removed 10-12 h after LMWH *and* 4 h prior to next dose; postpone LMWH 24 if traumatic	INR < 1.5 for performance of neuraxial techniques; no INR guidelines for catheter removal	Not discussed	Not discussed
American Society of Regional Anesthesia and Pain Medicine	No contraindication with NSAIDs; discontinue ticlopidine 14 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 8-48 h in advance	No contraindication, consider delaying heparin until after block if technical difficulty anticipated	Heparinize 1 h after neuraxial technique, remove catheter 2-4 h after last heparin dose; no mandatory delay if traumatic	Twice daily dosing: LMWH 24 h after surgery, regardless of technique; remove neuraxial catheter 2 h before first LMWH dose. Single daily dosing: according to European statements	Document normal INR after discontinuation (prior to neuraxial technique); remove catheter when INR ≤ 1.5 (initiation of therapy)	No data on safety interval for performance of neuraxial technique or catheter removal; follow fibrinogen level	No evidence for mandatory discontinuation prior to neuraxial technique; be aware of potential drug interactions

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; GP IIb/IIIa, platelet glycoprotein receptor IIb/IIIa inhibitors; INR, international normalized ratio; LMWH, low molecular weight heparin.

Data from the German Society of Anesthesiology and Intensive Care Medicine Consensus guidelines[77] and the Spanish Consensus Forum.[76]

pants. At least 2 other societies have approved official guidelines for thromboembolism prophylaxis and regional anesthesia. A comparison of the Spanish Consensus Statements[76] with those of the German Society of Anesthesiology and Intensive Care[77] and the ASRA reveals several similarities as well as differences (Table 6). The management of patients receiving unfractionated heparin is remarkably similar. As expected, the ASRA guidelines for LMWH are much more conservative than the corresponding European statements owing to the large number of hematomas in North America. It is notable that the Spanish Consensus Forum extensively analyzes the risk of spinal hematoma associated with all antiplatelet agents and recommends discontinuation of these medications prior to neuraxial block. It is somewhat difficult to justify this practice; the safety of neuraxial anesthesia in combination with antiplatelet therapy is well documented[11] and only 4 spinal hematomas in patients on NSAIDs have been reported.[26,105,107] In addition, nearly half of patients report preoperative antiplatelet therapy when questioned.[24] If a significant risk existed, one would expect more published reports of spinal hematoma among these patients. Conversely, more potent antiplatelet agents, including ticlopidine, clopidogrel, and abciximab, warrant increased caution. Revised ASRA guidelines recommend that neuraxial blocks be avoided in patients receiving these medications until platelet function has recovered. It is of interest that neither the Spanish nor the German Consensus Statements address the issue of neuraxial anesthesia in the patient receiving thrombolytics or herbal medications. Admittedly, although the pharmacology of thrombolytic agents is fairly well defined, few data are available to quantify the risk. Additional information is needed to allow evidence-based recommendations for patients reporting herbal therapy.

Unplanned Anticoagulation During Neuraxial Analgesia

Occasionally, patients require emergent antithrombotic therapy (vascular graft thrombosis, acute coronary syndrome/myocardial infarction), or a breakdown in communication results in unanticipated anticoagulation in the presence of indwelling epidural catheters. It is critical that the Pain Service be aware of alterations in the degree and timing of anticoagulation. Increasing centralization and computerization make it possible for Hospital Pharmacy Services to assist with patient management. Because all medication orders are filled by

pharmacists using a central computer, patients who receive an epidural infusion are identified within the pharmacy database. Any subsequent order for an antithrombotic agent is flagged as a drug "interaction" during entry, and the pharmacist receives an alert notice to contact the Pain Service. This "pharmacy failsafe" allows the Pain Service to participate proactively in the timing of catheter removal and subsequent anticoagulation, as well as closely monitor the patient's neurologic status.[144]

Plexus and Peripheral Block in the Anticoagulated Patient

Although spinal hematoma is the most significant hemorrhagic complication of regional anesthesia due to the catastrophic nature of bleeding into a fixed and noncompressible space, the associated risk following plexus and peripheral techniques remains undefined. There are no investigations that examine the frequency and severity of hemorrhagic complications following plexus or peripheral block in anticoagulated patients. However, few reports of serious complications following neurovascular sheath cannulation for surgical, radiological, or cardiac indications have been reported. For example, during interventional cardiac procedures, large bore catheters are placed within brachial or femoral vessels. Heparin, LMWH, antiplatelet medications, and/or thrombolytics are subsequently administered. In a series of 4,879 patients undergoing cardiac catheterization and/or coronary angioplasty, the frequency of vascular complications was 0.39%. Size of the catheter (5-French *v* 7-French) and degree of anticoagulation influenced the frequency of complications.[145] No neurologic complications occurred as a result of the vascular injury; 1 patient required transfusion.

Several cases of vascular injury with (or without) resultant nerve dysfunction have been described following plexus or peripheral techniques in patients with normal[146-149] and abnormal[15,16,150,151] hemostasis. In all patients with neurodeficits,[147,149,150] neurologic recovery was complete within 6 to 12 months. Thus, while bleeding into a neurovascular sheath may result in significant decreases in hematocrit, the expandable nature of peripheral site may decrease the chance of irreversible neural ischemia.

All cases of major bleeding associated with nonneuraxial techniques occurred after psoas compartment or lumbar sympathetic block. One patient with a mechanical heart valve had been therapeutically anticoagulated with warfarin and was converted to standard heparin in anticipation of knee arthroscopy. Coagulation status was normal at the time of psoas compartment block. However, a heparin infusion (and oral warfarin) was restarted 8 hours after needle placement. On the third postoperative day, the patient was noted to have markedly prolonged aPTT and elevated PT. CT performed to evaluate the patient's complaint of flank pain and ongoing reduction in hemoglobin (from 12.8 g/dL to 8.8 g/dL) noted a large hematoma arising from the psoas muscle. Vitamin K and 2 U blood were administered.[15]

Two of the cases associated with psoas compartment block received LMWH perioperatively. In 1 case, a continuous psoas block and single injection sciatic block were performed prior to knee arthroplasty. Although frank blood was noted in the psoas catheter, after partial withdrawal, aspiration and test dose were negative. Enoxaparin was administered 40 hours postoperatively; the catheter was removed 2 hours after LMWH injection, during peak anticoagulant effect. The patient complained of severe paravertebral pain 4 hours later, but remained neurologically intact. A CT scan demonstrated a large retroperitoneal hematoma. Her hemoglobin had decreased from 14.4 g/dL on admission to 7.1 g/dL, necessitating transfusion of 4 U red blood cells.[15] An additional LMWH-related hematoma occurred in a patient hospitalized with a calcaneal fracture.[150] Thromboprophylaxis was initiated with enoxaparin 30 mg twice daily. Surgical debridement had been previously performed twice under uneventful combined psoas-sciatic block. Approximately 20 hours after a dose of enoxaparin, she was brought to the operating room for a third procedure. Attempts at psoas needle placement were unsuccessful and traumatic. The following day, the patient complained of hip pain, which progressed to weakness. A retroperitoneal hematoma involving the psoas muscle was noted on CT. She gradually regained all sensory and motor function with conservative therapy.

Thienopyridine derivatives (ticlopidine and clopidogrel) were implicated in 2 cases of severe bleeding following lumbar sympathetic block.[16] The first patient underwent 2 lumbar sympathetic blocks. His medications included ticlopidine 500 mg/d. No coagulation testing was performed prior to needle insertion. After the first block, his hemoglobin decreased from 13.5 g/dL to 10.3 g/dL, and he complained of groin pain and medial thigh numbness. Vessel puncture occurred during performance of the second block 6 days later. The following night, he complained of severe groin pain, accompanied by a decrease in his blood pressure and hemoglobin (8.9 g/dL) due to a large retroperitoneal hematoma. The patient was transfused and achieved full recovery. The second patient underwent uneventful

lumbar sympathetic block. Her clopidogrel had been discontinued 3 days prior to the block; coagulation parameters, including bleeding time were normal. Nine hours later, she acutely complained of groin pain. The patient was found pulseless 3 hours later; attempts at resuscitation were unsuccessful. Autopsy revealed a 2 to 3 L hematoma in the psoas muscle.

These cases suggest that significant blood loss, rather than neural deficits, may be the most serious complication of non-neuraxial regional techniques in the anticoagulated patient. Additional information is needed to make definitive recommendations. Conservatively, the Consensus Statements on Neuraxial Anesthesia and Anticoagulation may be applied to plexus and peripheral techniques.[15] However, this may be more restrictive than necessary.

Practice guidelines or recommendations summarize evidence-based reviews. However, the rarity of spinal hematoma defies a prospective-randomized study, and there is no current laboratory model. As a result, these consensus statements represent the collective experience of recognized experts in the field of neuraxial anesthesia and anticoagulation. They are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding. An understanding of the complexity of this issue is essential to patient management; a "cookbook" approach is not appropriate. Rather, the decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, weighing the small, though definite risk of spinal hematoma with the benefits of regional anesthesia for a specific patient. Alternative anesthetic and analgesic techniques exist for patients considered an unacceptable risk. The patient's coagulation status should be optimized at the time of spinal or epidural needle/catheter placement, and the level of anticoagulation must be carefully monitored during the period of epidural catheterization. Indwelling catheters should not be removed in the presence of therapeutic anticoagulation, as this appears to significantly increase the risk of spinal hematoma. It must also be remembered that identification of risk factors and establishment of guidelines will not completely eliminate the complication of spinal hematoma. In Vandermeulen's series, although 87% of patients had a hemostatic abnormality or difficulty with needle puncture, 13% had no identifiable risk factor.[26] Vigilance in monitoring is critical to allow early evaluation of neurologic dysfunction and prompt intervention. We must focus not only on the prevention of spinal hematoma, but also optimization of neurologic outcome.

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