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Analgesia without paraplegia: Neuraxial anesthesia and anticoagulation

Terese T. Horlocker, M.D.*

* Professor of Anesthesiology. Mayo Clinic. Rochester, Minnesota.

An understanding of the mechanisms of blood coagulation, the pharmacologic properties of the anticoagulant and antiplatelet medications, and also the clinical studies involving patients undergoing central neural blockade while receiving these medications is paramount in reducing the risk of spinal hematoma in patients undergoing neuraxial blockade.

The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is unknown; however, the incidence cited in the literature is estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics (Tryba, 1993). In a review of the literature between 1906 and 1994, Vandermeulen et al (Vandermeulen, 1994). reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia. Included were five parturients and four patients with anatomic abnormalities of the spine, such as spina bifid occulta, spinal ependymoma, and spinal angioma. A spinal anesthetic was performed in 15 cases, the remaining received an epidural technique. In 42 of the 61 patients (68%), the spinal hematoma occurred in patients with evidence of hemostatic abnormality. Twenty-five patients had received intravenous heparin (18 patients), subcutaneous heparin (3 patients), or LMWH (4 patients), while an additional five patients presumably received heparin during 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 neuraxial anesthetic. Needle placement was reported as difficult in 25% of patients and/or bloody in 25% of patients. Multiple punctures were reported in 20% of patients. Therefore, in 87% of patients, a hemostatic abnormality or traumatic/difficult needle placement was present. More than one risk factor was present in 20 of 61 cases. Regional technique was also important. 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 eight hours of onset of neurologic dysfunction.

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 1990's (Cheney, 1999). Spinal hematomas accounted for nearly half of the spinal cord injuries. Risk factors for spinal hematoma included epidural anesthesia in the presence of intravenous 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.

It is impossible to conclusively determine risk factors for the development of spinal hematoma in patients undergoing neuraxial blockade solely through review of the case series, which represent only patients with the complication and do not define those who underwent uneventful neuraxial analgesia. However, large inclusive surveys that evaluate the frequencies of complications (including spinal hematoma), as well as identify subgroups of patients with higher or lower risk, enhance risk stratification. Moen et al. (Moen, 2004) investigated serious neurologic complications among 1,260,000 spinal and 450,000 epidural

blocks performed in Sweden over a ten-year period. Among the 33 spinal hematomas, 24 occurred in females; 25 were associated with an epidural technique. A coagulopathy (existing or acquired) was present in 11 patients; two of these patients were parturients with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Pathology of the spine was present in six patients. The presenting complaint was typically lower extremity weakness. Only five of 33 patients recovered neurologically (due to delay in the diagnosis/intervention). These demographics, risk factors and outcomes confirm those of previous series. However, the methodology allowed for calculation of frequency of spinal hematoma among patient populations. For example, the risk associated with epidural analgesia in women undergoing childbirth was significantly less (1 in 200,000) than that in elderly women undergoing knee arthroplasty (1 in 3,600, $p < 0.0001$). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (1 in 22,000) compared to all patients undergoing spinal anesthesia (1 in 480,000).

Overall, these series suggest that the risk of clinically significant bleeding varies with age (and associated abnormalities of the spinal cord or vertebral column), the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation (particularly with standard heparin or LMWH); perhaps in a multifactorial manner. They also consistently demonstrate the need for prompt diagnosis and intervention.

Neurologic outcome in patients with spinal hematoma following neuraxial blockade*

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

*Neurologic outcome was reported for 55 of 61 cases of spinal hematoma following neuraxial blockade
Adapted from Vandermeulen et al.

ORAL ANTICOAGULANTS

Few data exist regarding the risk of spinal hematoma in patients with indwelling epidural catheters who are anticoagulated with warfarin. The optimal duration of an indwelling catheter and the timing of its removal also remain controversial. To date, only three studies have evaluated the risk of spinal hematoma in patients with indwelling spinal or epidural catheters who receive oral anticoagulants perioperatively. Odoom and Sih (Odoom, 1996) performed 1,000 continuous lumbar epidural anesthetics in vascular surgical patients who were receiving oral anticoagulants preoperatively. The thrombotest (a test measuring factor IX activity) was decreased in all patients prior to needle placement. Heparin was also administered intraoperatively. Epidural catheters remained in place for 48 hours postoperatively. There were no neurologic complications. While these results 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 the usefulness of these results. Therefore, except in extraordinary circumstances, spinal or epidural needle/catheter placement and removal should not be performed in fully anticoagulated patients.

There were also no symptomatic spinal hematomas in 192 patients receiving postoperative epidural analgesia in conjunction with low-dose warfarin after total knee arthroplasty. Patients received warfarin, starting on the postoperative day, to prolong the PT to 15.0-17.3 s (normal 10.9-12.8 s), corresponding to an INR of 2.0-3.0. Epidural catheters were left indwelling 37 ± 15 h (range 13-96 h). Mean PT at the time of epidural catheter removal was 13.4 ± 2 s (range 10.6-25.8 s). The mean PT did not increase beyond the normal range until 48 hours postoperatively, and therapeutic values were not achieved on average until the seventh postoperative day. This study documents the relative safety of low-dose warfarin anticoagulation in patients with an indwelling epidural catheter. It also demonstrates the large variability in patient response to warfarin. For example, the mean PT did not increase beyond the normal range until 48 hours postoperatively, and therapeutic values were not achieved on average until the seventh postoperative day. However, 36 patients had a documented PT greater than 12.8 s after a single dose of warfarin, including 2 patients with therapeutic values. The authors recommended close monitoring of coagulation status to avoid excessive prolongation of the PT during epidural catheterization (Horlocker, 1994).

Wu and Perkins (Wu, 1996) retrospectively reviewed the medical records of 459 patients who underwent orthopedic surgical procedures under spinal or epidural anesthesia, including 412 patients who received postoperative epidural analgesia. Preoperatively, antiplatelet medications were reported in 270 patients, warfarin (mean dose 4.9 ± 1.4 mg) in 181 patients, subcutaneous (unfractionat-

ed) heparin in 5 patients, and LMWH in 6 patients. All patients were anticoagulated with warfarin postoperatively, although the dose of warfarin administered was not recorded. The time of catheter removal and corresponding PT were noted. Mean duration of epidural analgesia was 43.6 ± 12.5 hours (range 5-118 hours). Prothrombin time at the time of epidural catheter removal was 14.1 ± 3.2 s (normal 9.6-11.1 s), corresponding to an INR of 1.4. Patients who had warfarin thromboprophylaxis initiated preoperatively had significantly higher PTs at the time of catheter removal than patients who had received postoperative warfarin only. There was no evidence of spinal hematoma. These results suggest that patients receiving oral anticoagulants may safely undergo regional techniques, even when thromboprophylaxis is initiated preoperatively. Unfortunately, this study reports only the PT at the time of catheter removal, and does not describe the prolongation of the PT with respect to progressive warfarin administration, making it impossible to determine how many doses of warfarin and what cumulative dose will result in thromboprophylactic effect.

Regional anesthetic management of the patient on oral anticoagulants

Anesthetic management of patients anticoagulated perioperatively with warfarin is dependent on dosage and timing of initiation of therapy. Since factor VII has a relatively short half-life, prolongation of the PT and INR may occur in 24-36 hours after initiation of warfarin therapy. The PT will be prolonged (outside of normal range) when factor VII activity is reduced to approximately 55% of baseline. However, the therapeutic effect of warfarin anticoagulation is most dependent on reduction in factors II and X activity. Since these factors have circulating half-lives of 36-48 and 72-96 hours respectively, thromboprophylaxis is not adequate for 3-5 days after starting warfarin therapy.

Many orthopedic surgeons administer the first dose of warfarin the night before surgery. For these patients, the PT and 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 and INR monitored on a daily basis, and checked before catheter removal, if initial dose of warfarin was more than 36 hours beforehand. Reduced doses of warfarin should be given to patients who are likely to have an enhanced response to the drug. In general, is it recommended that indwelling neuraxial catheters be removed when the INR < 1.5 in order to assure adequate levels of all vitamin-K dependent factors. An INR > 3 should prompt the physician to withhold or reduce the warfarin dose in patients with indwelling neuraxial catheters. There is no definitive recommendation for removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during a neuraxial catheter infusion.

The PT and INR of patients on chronic oral anticoagulation will require three to five days to normalize after warfarin discontinuation. Theoretically, since the PT and INR reflect predominantly factor VII activity, (and factor VII has only a six to eight hour half-life), there may be an interval during which the PT and INR approach normal values, yet factors II and X levels may not be adequate for normal hemostasis. Adequate levels of all vitamin K-dependent factors are typically present when the INR is in the normal range. Therefore, it is recommended that documentation of the patient's normal coagulation status be achieved prior to implementation of neuraxial block (Horlocker, 1994).

INTRAVENOUS AND SUBCUTANEOUS STANDARD HEPARIN

Complete systemic heparinization is typically reserved for the most high-risk patients, typically patients with an acute thromboembolism. However, intraoperative administration of a modest intravenous dose is occasionally performed during vascular or orthopedic procedures. In a study involving over 4,000 patients, Rao and El-Etr (Rao, 1981) demonstrated the safety of indwelling spinal and epidural catheters during systemic heparinization. However, the heparin activity was closely monitored, the indwelling catheters were removed at a time when circulating heparin levels were relatively low, and patients with a preexisting coagulation disorder were excluded. A subsequent study in the neurologic literature by Ruff and Dougherty (Ruff, 1981) reported spinal hematomas in 7 of 342 patients (2%) who underwent a diagnostic lumbar puncture and subsequent heparinization. Traumatic needle placement, initiation of anticoagulation within 1 hour of lumbar puncture or concomitant aspirin therapy were identified as risk factors in the development of spinal hematoma in anticoagulated patients. 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. 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 extreme vigilance is necessary to diagnose and intervene as early as possible, should spinal hematoma be suspected (Cheney, 1999).

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 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

From Stafford-Smith. Impaired haemostasis and regional anaesthesia. Can J Anaesth 1996:43:R129-41.

The use of epidural and spinal anesthesia and analgesia in the presence of high dose intraoperative systemic heparin, specifically in cardiac surgery has gained recent popularity. In a recent survey of the membership of the Society of Cardiovascular Anesthesiologists, Goldstein et al surveyed 3974 cardiac anesthesiologists, and found 7% of their responders used spinal or epidural techniques for cardiac surgery (Goldstein, 2001). Interestingly, the majority of anesthesiologists would proceed if frank blood was noted in the spinal or epidural needle. To date there are no case reports of spinal hematomas associated with this technique published or within the Closed Claims Project (Cheney, 1999). Ho et al calculated the risk of hematoma among these patients. In a complex mathematical analysis of the probability of predicting a rare event that has not occurred yet, they estimate the probability of an epidural 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 injection, and 1:3,610 for spinal technique (Ho, 2000).

Low-dose subcutaneous standard (unfractionated) heparin is administered for thromobprophylaxis in patients undergoing major thoracoabdominal surgery and in patients at increased risk of hemorrhage with oral anticoagulant or LMWH therapy. As previously mentioned, subcutaneous heparin does not provide adequate prophylaxis following major orthopedic surgery, and is seldom utilized in this patient population. A review of the literature by Schwander and Bachmann (Schwander, 1991) noted no spinal hematomas in over 5,000 patients who received subcutaneous heparin in combination with spinal or epidural anesthesia. There are only three cases of spinal hematoma associated with neuraxial blockade in the presence of low-dose heparin, two of which involved a continuous epidural anesthetic technique (Vandermeulen, 1994).

Regional anesthetic management of the patient receiving standard heparin

The safety of neuraxial techniques in combination with intraoperative heparinization is well documented, providing no other coagulopathy is present. 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.

Intravenous heparin administration should be delayed for 1 hour after needle placement. Indwelling catheters should be removed 1 hour before a subsequent heparin administration or 2-4 hours after the last heparin dose. Evaluation of the coagulation status may be appropriate prior to catheter removal in patients who have demonstrated enhanced response or are on higher doses of heparin. Although the occurrence of a bloody or difficult needle placement may increase risk, there are no data to support mandatory cancellation of a case should this occur. If the decision is made to proceed, full discussion with the surgeon and careful postoperative monitoring are warranted.

Prolonged therapeutic anticoagulation appears to increase risk of spinal hematoma formation, especially if combined with other anticoagulants or thrombolytics. Therefore, neuraxial blocks should be avoided in this clinical setting. If systematic anticoagulation therapy is begun with an epidural catheter in place, it is recommended to delay catheter removal for 2-4 hours following heparin discontinuation and after evaluation of coagulation status.

There is no contradiction to use of neuraxial techniques during subcutaneous standard heparin. 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 or after prolonged therapy. A platelet count is indicated for patients receiving subcutaneous heparin for greater than 5 days (Horlocker, 2003).

LOW MOLECULAR WEIGHT HEPARIN

Enoxaparin, 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. Within one year, two cases of spinal hematoma had been voluntarily reported through the MedWatch system. Despite repeated efforts at relabeling and education, cases of spinal hematoma continued to occur. A total of 30 cases of spinal hematoma in patients undergoing spinal or epidural anesthesia while receiving LMWH perioperatively were reported between May 1993 and November 1997. An FDA Health Advisory was issued in December 1997. In addition, the manufacturers of all LMWH and heparinoids were requested to revise the labeling of their respective products, and place a black «boxed warning».

At the time of the Consensus Conference on Neuraxial Anesthesia and Anticoagulation on April 1998, there were 45 cases of spinal hematoma associated with LMWH, 40 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. Median time interval between initiation of LMWH therapy and neurologic dysfunction was three days, while median time to onset of symptoms and laminectomy was over 24 hours. Less than one third of the patients reported fair or good neurologic recovery (Horlocker, 1998).

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 to 1 in 40,000 spinal anesthetics (Schroeder, 1998). 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.

There have been only 13 cases of spinal hematoma following neuraxial block since 1998 reported through the MedWatch system or published as case reports. In addition to LMWH, five patients received ketorolac, one patient received ibuprofen, and one patient received intravenous unfractionated heparin during a vascular procedure. The regional technique was a spinal anesthetic in three cases. The remaining ten 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.

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 (Geerts, 2004). 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 fibrillation, or preexisting hypercoagulable condition. The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher. Needle placement should occur a minimum of 24 hours following this level of LMWH anticoagulation.

Anesthetic management of the patient receiving low molecular weight heparin

Perioperative management of patients receiving LMWH requires coordination and communication. Time intervals between neuraxial needle placement and administration of LMWH must be maintained. 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 (McEvoy, 2000) 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 institution, rather than deviate from the routine.

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. The presence of blood during needle and catheter placement does not necessitate postponement of surgery.

Preoperative LMWH. Patients on preoperative LMWH can be assumed to have altered coagulation. A single-injection spinal anesthetic may be the safest neuraxial technique

in patients receiving preoperative LMWH for thromboprophylaxis. In these patients needle placement should occur at least 10-12 hours after the LMWH dose. Patients receiving treatment doses of LMWH will require delays of at least 24 hours. Neuraxial techniques should be avoided in patients administered a dose of LMWH two 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. 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 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 two hours after catheter removal.

ANTIPLATELET MEDICATIONS

Antiplatelet medications are seldom used as primary agents of thromboprophylaxis. However, many orthopedic patients report chronic use of one or more antiplatelet drugs (Horlocker, 1995). Although Vandermeulen et al (Vandermeulen, 1994) implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia, several large studies have demonstrated the relative safety of neuraxial blockade in both obstetric, surgical and pain clinic patients receiving these medications (Horlocker, 1995; CLASP, 1994; Horlocker, 2002). In a prospective study involving 1000 patients, Horlocker et al (Horlocker, 1995) reported that preoperative antiplatelet therapy did not increase the incidence of blood present at the time of needle/catheter placement or removal, suggesting that trauma incurred during needle or catheter placement is neither increased nor sustained by these medications. The clinician should be aware of the possible increased risk of spinal hematoma in patients receiving antiplatelet medications who undergo subsequent heparinization (Ruff, 1981).

Ticlopidine and clopidogrel are also platelet aggregation inhibitors. These agents interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect is irreversible for the life of the platelet. Ticlopidine and clopidogrel have no effect on platelet cyclooxygenase, acting independently of aspirin. However, these medications have not been tested in combination. Platelet dysfunction is present for 5-7 days after discontinuation of clopidogrel and 10-14 days with ticlopidine.

Platelet glycoprotein IIb/IIIa receptor antagonists, including abciximab (Reopro®), eptifibatide (Integrilin®) and tirofiban (Aggrastat®), inhibit platelet aggregation by interfering with platelet-fibrinogen binding and subsequent platelet-platelet interactions. Time to normal platelet aggregation following discontinuation of therapy ranges from eight hours (eptifibatide, tirofiban) to 48 hours (abciximab).

Increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists (Kovesi, 2002) warrants concern regarding the risk of anesthesia-related hemorrhagic complications.

Regional anesthetic management of the patient receiving antiplatelet medications

Antiplatelet drugs, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. However, the concurrent use of medications that affect other components of the clotting mechanisms, such as oral anticoagulants, standard heparin, and LMWH, may increase the risk of bleeding complications for patients receiving antiplatelet agents. Assessment of platelet function prior to performance of neuraxial block is not recommended. However, careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial.

The increase in perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel and platelet GP IIb/IIIa antagonists warrants concern regarding the risk of spinal hematoma. The recommended time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. For the platelet GP IIb/IIIa inhibitors, the duration ranges from eight hours for eptifibatide and tirofiban, to 48 hours following abciximab administration (Horlocker, 2003).

HERBAL MEDICATIONS

There is a widespread use of herbal medications in surgical patients. 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. Because 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.

Garlic. 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. Although these effects have not been consistently demonstrated in volunteers, there is one case in the literature of an octagenarian who developed a spontaneous epidural hematoma that was attributed to heavy garlic use (Rose, 1990).

Ginkgo. Ginkgo is derived from the leaf of Ginkgo biloba. Ginkgo inhibits platelet-activating factor. Clinical trials in a small number of patients have not demonstrated bleeding complications, but four reported cases of spontaneous intracranial bleeding and one case of spontaneous hyphema have been associated with ginkgo use. Based upon the pharmacokinetic data, normalization of coagulation should occur 36 hours after discontinuation of ginkgo (Chung, 1987).

Ginseng. There is a concern of ginseng's effect on coagulation pathways. Ginsenosides inhibit platelet aggregation in vitro and prolong both thrombin time and activated partial thromboplastin time in rats. 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 one reported case (Janetzky, 1997). The pharmacokinetics of ginsenosides suggest that 24 hours is required to allow resolution of ginseng's effect on hemostasis.

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 since it is likely that a significant number of our surgical patients utilize alternative medications preoperatively and perhaps during their postoperative course. There is no wholly accepted test to assess adequacy of hemostasis in the patient reporting preoperative herbal medications. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. 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 (Horlocker, 2003).

THROMBOLYTIC AND FIBRINOLYTIC THERAPY

Thrombolytic agents actively dissolve fibrin clots that have already formed. Exogenous plasminogen activators such as streptokinase and urokinase, not only dissolve thrombus but also affect circulating plasminogen as well, leading to decreased levels of both plasminogen and fibrin. Recombinant tissue-type plasminogen activator (rt-PA), an endogenous agent, is more fibrin-selective and has less effect on circulating plasminogen levels. 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 intravenous heparin to maintain an APTT of 1.5 to 2 times normal and clopidogrel/aspirin. No controlled studies have examined the risk. Several cases of spinal hematoma in patients with indwelling epidural catheters who received thrombolytic agents have been reported in the literature.

Regional anesthetic management of the patient on thrombolytics and fibrinolytics

The physiologic state induced by the use of fibrinolytic and thrombolytic agents represents a unique problem in the performance of regional anesthesia. Patients receiving concurrent heparin with fibrinolytic and thrombolytic drugs are at high risk of adverse neuraxial bleeding during spinal or epidural anesthesia. Patients receiving fibrinolytic and thrombolytic drugs should be cautioned against receiving spinal or epidural anesthetics except in highly unusual circumstances. Guidelines detailing original contraindications for thrombolytic drugs suggest avoidance of these drugs within 10 days of puncture of noncompressible vessels. Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.

Neurologic monitoring needs to be carried out 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 blockade. There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. Caution must be exercised in making decisions about removing or maintaining these catheters. The measurement of fibrinogen may be helpful in making a decision about catheter removal or maintenance (Horlocker, 2003).

FONDAPARINUX

Fondaparinux, a synthetic pentasaccharide, was approved in December 2001. The FDA released fondaparinux (Arix-

tra®) 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 six hours postoperatively. Investigators reported a spinal hematoma among the initial dose-ranging study (at a dose that was subsequently determined to be twice required for thromboprophylaxis) (Landow, 1997, Turpie, 2001). 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 two hours prior to fondaparinux administration (Turpie, 2001). 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 (Horlocker, 1995).

Anesthetic management of the patient receiving fondaparinux

Although the actual risk of spinal hematoma with fondaparinux is unknown, we believe extreme caution is warranted given the sustained antithrombotic effect, early postoperative dosing, and "irreversibility". 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 utilized. Close monitoring of the surgical literature for risk factors associated with surgical bleeding may be helpful in risk assessment and patient management (Horlocker, 2003).

New antithrombotic drugs that 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. Furthermore, since the risk of thromboembolic complications is deceased with intraoperative or early postoperative initiation of antithrombotic therapy, it is anticipated that the new pharmacologic therapies will utilize these principles.

TRENDS IN THROMBOPROPHYLAXIS THAT MAY INCREASE RISK OF SPINAL HEMATOMA

- High risk general surgery patients (those greater than 40 years of age undergoing a major procedure) are recommended to receive unfractionated heparin subcutaneously (SC) every *eight* hours. It is likely that a significant number of patients will be therapeutically anticoagulated for a brief time.
- Fondaparinux is recommended as an anti-thrombotic agent following major orthopedic surgery. The extended half-life (approximately 20 hours) allows once daily dosing, which also impedes safe catheter removal.
- The target international normalized ratio (INR) for warfarin therapy following total joint replacement is 2.5 (range 2.0-3.0). This is considerable higher than the level achieved by many orthopedists, and if adapted would necessitate earlier removal (or avoidance) of epidural catheters.
- Thromboprophylaxis is often administered in close proximity to surgery. Unfortunately, early postoperative dosing is associated with surgical (and often anesthesia-related) bleeding.
- The duration of prophylaxis has been extended to a minimum of ten days following total joint replacement or hip fracture surgery and 28-35 days for hip procedures. It has been demonstrated that the risk of bleeding complications is increased with the duration of anticoagulant therapy.

In summary, the decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving anticoagulants perioperatively 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 to be at 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. It is important to note that patients respond with variable sensitivities to anticoagulant medications. Indwelling catheters should not be removed in the presence of therapeutic anticoagulation, as this appears to significantly increase the risk of spinal hematoma. In addition, communication between clinicians involved in the perioperative management of patients receiving anticoagulants is essential in order to decrease the risk of serious hemorrhagic complications.

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