Anticoagulants and Regional Anesthesia

Michael Paech, FANZCA

Although uncontrolled bleeding may present problems after several regional blocks, this review will focus on intraspinal hematoma following central neural blockade (CNB) and its association with anticoagulant therapy. The epidural space contains a rich venous plexus compared with the low vascularity of the subarachnoid space, making epidural more common than subdural or subarachnoid hematoma. Anatomical self-tamponade and hemostatic control probably account for the low incidence despite frequent epidural venous injury (>10% in some obstetric series). With anticoagulants, uncontrolled bleeding may generate high pressure in an area of low compliance, and risk pressure or ischemic injury to the central neuraxis.

Early diagnosis and short time to treatment (usually surgical decompression, preferably within eight hours of the development of paraplegia) are critical to full resolution of neurological deficit.[1-3] Staff, especially nursing, must be educated to maintain a high index of diagnostic suspicion. Monitoring of neurological function, especially during epidural analgesia (ideally conducted with minimal motor block), is important if hematoma are to be detected early. Presentation varies, commonly involving new neurological changes, especially muscle weakness, bowel or bladder dysfunction; or unexpected delay in resolution of, or inappropriately dense, motor block. Acute back pain and sensory deficits are frequent.[2] Magnetic resonance imaging is the most effective diagnostic tool, but computerised tomography or myelography must be considered if MRI is not readily available.

Recommendations will be made to guide clinical practice. These carry the caveat that they are almost all based on level 3 or 4 evidence and not evidence from randomized trials or meta-analysis. In some areas (eg. CNB and low molecular weight heparin or full anticoagulation for cardiac surgery), consensus views are still being formulated.

Spinal Hematoma and Central Neural Blockade (CNB)

Regional anesthesia and analgesia has many advantages in obstetrics and a variety of surgical specialties, especially orthopedics. Level 3 evidence exists for reduced maternal mortality in obstetrics and level 1 & 2 evidence for reduced post-surgical morbidity (eg. reduced blood loss and thromboembolism with hip replacement; improved outcome in peripheral vascular surgery; and more rapid recovery and rehabilitation after colonic and major knee surgery).[4]

Regional anesthesia is frequently contemplated for patients receiving anticoagulant drugs. Orthopedic patients often take analgesic drugs with antiplatelet activity, and the medical use of antiplatelet therapy for cerebrovascular and cardiac disease has increased dramatically. Many patients who benefit from regional block also warrant pharmacological thromboembolism prophylaxis, frequently with heparin. Combined warfarin and regional anesthesia may potentiate the thromboprophylactic effect. Other patients receive therapeutic anticoagulation because of previous thromboembolism or for various cardiac conditions. Because of advantages related to ischemic events, surgical outcome and postoperative recovery, CNB is being used increasingly for vascular and cardiac surgery despite systemic heparinization. The potential to safely combine CNB with anticoagulant drugs is thus important in numerous settings, and our understanding and knowledge of risk continues to change.

Spontaneous vertebral canal hematoma is estimated to occur at a rate of 1: 1,000,000 per year. Because of its rarity, quantification of hematoma in association with CNB is very difficult and the incidence is unknown. A prospective trial is unlikely to be feasible, because to achieve adequate power more than 100,000 patients would required. Many complication-free series, totalling over 200,000 patients, have been published.[2] One review of 20 series estimated an incidence of 1:150,000 for epidural and 1:220,000 for spinal block,[1] while another review of 34 series of epidurals estimated 1;190,000.[5] However, these are probably underestimates and a recent prospective review of almost 18,000 CNBs reported three hematoma (all anticoagulated patients having epidural analgesia).[6]

Epidural hematoma is now the most common mechanism of spinal cord injury in the American Society of Anesthesiologists Closed Claims Project Database and spinal cord injury is the leading cause of claims for nerve injury.[3] Reviews of case reports to identify risk factors

indicate an important association between hematoma and disordered hemostasis, in particular concurrent anticoagulant drug therapy (table 1). For example, 30 of 61 cases between 1906-1994, and 25 of 51 cases identified between 1966-1995, involved anticoagulants, especially intravenous unfractionated heparin (UH).[2, 5] A review of case reports of hematoma after lumbar puncture from 1911-1994 found that 15 of 33 cases involved anticoagulant (n=13) or antiplatelet drugs (n=2).[7]

Table 1: Risk Factors for Spinal Hematoma

a. None (33%)	Patient Factors (21%)	Drugs (54%)[a] *iv* heparin 26% *sc* heparin 13% Antiplatelet 7% Thrombolytic 3% Other 5%
b.	Patient Factors (51%)	Drugs (49%)[b] *iv* heparin 35% *sc* heparin 4% Antiplatelet 6% Thrombolytic 4%

[a] *Vandermeulen et al (ref. 2);* [b] *Wulf H (ref. 5)*

Frequently reported possible factors include multiple or traumatic needle insertion,[2,3,5,7] and epidural catheterisation compared with single-shot spinal technique[3,5,8] (Table 2). Removal of epidural catheters may be traumatic and coagulation status at the time appears as important as that at insertion, with 60-70% of hematoma occurring after removal.[2,5]

Table 2: Central Neural Blockade technique associated with Intraspinal Hematoma

	Epidural	**Spinal**
[a]Epidural catheter	20	0
Epidural needle only	1	0
Spinal catheter	0	1
Single-shot spinal	1	6
[b]Epidural catheter	32	
Single-shot spinal	15	
Epidural needle only	6	
Unknown	8	

[a] *Schmidt et al (ref. 8);* [b]*Vandermeulen et al (ref. 2)*

Hematoma and Oral Anticoagulants

The coumarins (eg. warfarin) are vitamin K antagonists that lead to production of coagulation factors II, VII, IX and X, and protein S and C, deficient in y-carboxyglutamic acid. Their inability to chelate calcium prevents binding to phospholipid membranes and thus to decreased prothrombin activation. Although the effect is not apparent until sufficient deficient factors have been synthesised, factor VII and protein C have short half-lives of 6-8 h, so prolongation of coagulation studies may be seen within 24-36 h. The more important effect, on Factors II & X, is not depressed until 4 - 6 days and after cessation of warfarin effects may persist for a similar duration.

There is limited data on CNB in the presence of warfarin. In general, Level 4 evidence (expert consensus) plus level 3 evidence (based on full anticoagulation with heparin) is that CNB, except in exceptional circumstances, should be avoided after therapeutic anticoagulation with warfarin [2,9,10].

Although the level of risk with minor derangement of coagulation parameters is unknown, evidence indicates it is not unacceptably high and individual cost-benefit assessment seems reasonable. In a study of 1,000 epidural blocks for 950 vascular procedures, all patients had received preoperative warfarin with documented anticoagulation. Intraoperative heparin was administered, but not continued, and all epidural catheters were removed at 48 h postoperatively. No hematoma occurred.[11] A retrospective review noted 192 epidural blocks in 188 orthopedic patients, some of whom were also on aspirin or had “bloody taps”. Low dose warfarin was commenced postoperatively and catheters maintained for up to 4 days. Although most patients had no increase in prothrombin time at the time of catheter removal, 36 showed an increase after only one dose of warfarin. No hematoma occurred either in this review[12] or in another retrospective review of 459 patients, 180 of whom were commenced on warfarin preoperatively, some whilst receiving antiplatelet drugs.[13] Most patients had a PT outside the normal range at the time of catheter removal. In the large series by Dahlgren et al, one of three hematoma involved a patient receiving dicoumarol.[6]

Nevertheless, caution is required. Seven of 33 cases of spinal hematoma after attempted lumbar puncture were associated with warfarin administration, usually commenced after difficult lumbar puncture and often in conjunction with heparin.[7] Several case reports describe hematoma following catheter removal, despite only modest changes in coagulation tests or with co-administration of other anticoagulant drugs.[10]

Hematoma and Antiplatelet Drugs

These commonly prescribed drugs include aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and other agents (eg. ticlopidine). Aspirin causes irreversible acetylation of platelet cyclo-oxygenase, blocking production of thromboxane A_2, a facilitator of secondary platelet aggregation and release reactions. The primary platelet plug may be fragile and platelet function is affected for the duration of its lifetime (7-10 days). Nonsteroidal anti-inflammatory drugs have a similar but reversible effect,

lasting a shorter time according to the duration of their pharmacokinetic action. Normal responses can be expected within 1-3 days of their cessation. Ticlopidine, like aspirin, has a prolonged effect after cessation.

Given the frequency of use and the very few case reports of hematoma in association with CNB, risk appears extremely low.[14] Examples include spontaneous hematoma in association with excessive aspirin ingestion[14] and concurrent antiplatelet drug use in 2 of 34 cases of hematoma after lumbar puncture[7] and 4 of 61 cases after epidural or spinal anaesthesia.[2]

In a retrospective review of 1013 CNBs, 39% of patients were receiving antiplatelet drugs and 11% multiple anticoagulant medications, but no hematoma were seen. The same authors then prospectively evaluated 924 patients having 1000 CNBs for orthopedic surgery. 386 were receiving antiplatelet drugs, including 22 with preoperative UH and 36 had abnormal coagulation tests. One fifth had a traumatic "bloody tap" insertion, without any increase in minor hemorrhagic complications and no hematoma.[15] In another prospective series, 87 patients receiving various aspirin doses received 246 CNBs with no sequele. The CLASP study of obstetric patients included over 3,000 in whom epidural analgesia was uncomplicated, although 1,422 were taking low-dose aspirin therapy.[16]

Again, this prospective data is of limited value. The 95% confidence interval for risk in the series by Horlocker et al[15] is >1%. Although greater caution appears warranted if other risk factors are present, especially concurrent heparin, level 3 & 4 evidence supports a very low risk with drugs having antiplatelet activity.[9,14,15]

Hematoma and Thrombolytic Drugs

Drugs such as urokinase, streptokinase and t-PA are plasminogen activators that permit cleavage of this inactive precursor to plasmin. By overwhelming inhibitory controls, they lyse both pathologic and hemostatic thrombi. Information is scarce about these drugs in association with CNB, although detailed recommendations exist.[17] In several case reports, hematoma occurred rapidly when thrombolytic drug were administered shortly after CNB[17] and, based on their ability to lyse existing clots, risk appears very high.

Hematoma and Intravenous Unfractionated Heparin (UH)

Unfractionated heparin (UH) is a negatively charged water-soluble acid mucopolysaccharide that is heterogenous with respect to molecular weight, anticoagulant properties and pharmacokinetic behaviour. An unique pentasaccharide present in some molecules binds and catalyzes antithrombin III, a slow-acting plasma serine protease inhibitor. This complex inhibits several procoagulant serine proteases, including thrombin (IIa), Xa and to a lesser extent IXa, XIa and XIIa. Inhibition of Xa and positive feedback loops via factors V and VIII also reduces thrombin production. After IV administration effects are immediate, the dose-dependent half life usually 1-2 hours, and clearance by hepatic, renal and endothelial mechanisms.

The ability to combine CNB with systemic heparin may be of value to postoperative outcome, especially for vascular surgery. Low-dose IV heparin (< 2000 IU) is effective prophylaxis in high-risk orthopedic patients and does not significantly alter hemostasis.

It appears that CNB in association with therapeutic or full anticoagulation with IV heparin (particularly if poorly managed) carries a significant risk of hematoma.[18] In older retrospective series that fail to report doses and monitoring, 8 of 509 patients receiving therapeutic IV heparin after lumbar puncture became paraplegic.[19,20] There are case reports of hematoma after epidural catheter removal while patients were heparinized, and two large reviews identified IV heparin as the major risk factor where drugs were implicated.[2,5] In a recent series, 2 of 3 hematoma in 9,234 epidural blocks involved IV heparin.[6] In the ASA Closed Claims analysis, 13 of 21 spinal cord injuries (11 epidurals and 2 spinals) were in patients anticoagulated with heparin.[3] In two thirds, postoperative care was judged to have been inappropriate, with signs and symptoms of hematoma being missed.

On the other hand, despite the lack of randomized trials, extensive clinical experience supports the relative safety of combining systemic anticoagulation and CNB, providing guidelines are followed and monitoring of heparinisation is meticulous. Baron et al retrospectively reviewed 912 peripheral vascular surgical patients heparinized to modest therapeutic levels after epidural block, and found no complications.[21] Similarly, Rao et al described 3,164 patients having continuous epidural analgesia and 847 having spinal anesthesia for vascular surgery, in whom IV heparin was commenced about 1 hour post-CNB and activated partial thromboplastin time (APTT) kept about twice normal.[22] These data, and those from many other small series,[18] are reassuring, and acceptance of this approach widespread. Nevertheless, the upper level of risk of hematoma calculated from the Rao study[22] is still as high as 0.35% (3 per 1000).

Full anticoagulation associated with CNB has been reported uneventfully in small numbers of chronic pain patients and in over a 1,000 cardiac surgical patients.[18] In association with cardiopulmonary bypass, both prospective and retrospective studies involving several hundred patients have not reported hematoma.[23] Further prospective data are required in this setting, as the level of risk cannot currently be determined.

Hematoma and Prophylactic Subcutaneous UH

Unfractionated hparin, 5000 u *sc* (bd or tds according to risk level) for thromboembolism prophylaxis has an onset from 1 hour and peak plasma levels occur at 2-4 hours.

Bioavailability varies widely due to protein and tissue binding, such that some patients develop measurable changes in APTT and up to 5% have therapeutic plasma levels for up to 4 hours.[18]

There are very few case reports of hematoma[18] and very low risk is suggested by the small proportion of cases compared with other anticoagulant drugs.[2,5] A French review of over 5,000 cases[18] and many series involving more than 9,000 patients found no major complications.[24] Surveys conducted in several countries indicate it is routine practice to combine *sc* low dose heparin and CNB.[18] Used appropriately, as outlined below, level 3 & 4 evidence thus indicates that the combination of low dose prophylactic SC UH and CNB does not confer a significant risk.[5,9,18]

Hematoma and Low Molecular Weight Heparins (LMWHs)

Compared with UH, the LMWHs (eg. enoxaparin and dalteparin) provide superior prevention of thromboembolism in certain high-risk patients and, although dose-dependent, reduce bleeding complications in general surgical patients.[25] Level 3 & 4 evidence suggests that, despite the current controversy outlined below, the combination of CNB and LMWH is acceptable provided recommendations are followed.

The LMWHs differ from UH in several respects. They have mean molecular weight of 4,000-6,500 Daltons (compared with approximately 15,000) and higher and more predictable bioavailability (90%), with half lives two to four times greater (3-6 h). This allows possible once daily dosing schedules. Peak activity occurs at about three hours, with anti-Xa activity still 50% after 12 hours. Clearance is predominantly renal and the risk of induced thrombocytopenia lower. The inhibitory effect on factor Xa is retained with relatively less thrombin inhibition. There is greater inhibition of the binding of fibrinogen to platelets and platelets to endothelium. Independent of platelet action, LMWHs increase tissue plasminogen activator and B-ß 14-52 related peptide levels, leading to profibrinolytic activity.[26]

These properties mean that dose adjustment and monitoring are not usually required. Standard coagulation tests are unaltered, and monitoring of anti-Xa and IIa activity is not usually or readily available, but can be considered in selected cases such as elderly patients with renal impairment. The thromboelastogram (TEG) is an alternative monitor, but is neither readily available nor validated. Reversal of anticoagulant effect with protamine is only partial (only anti-IIa activity is fully reversed) and activity may return.

Practice guidelines for *sc* UH cannot be applied to LMWHs. Nevertheless, guidelines for LMWH and CNB were first published in 1991 and European experience from 1987-1992 reviewed by Bergqvist et al was favourable.[27] No hematoma occurred in over 9,000 patients enrolled in clinical trials and only one case was reported in an estimated more than 1 million patients. In the USA, reports of hematoma appeared soon after the release of enoxaparin in 1993, and continued despite warnings. In December 1997, after more than 30 reports of hematoma associated with enoxaparin and CNB, the Federal Drug Authority in the USA issued a Public Health Advisory message. Most hematoma occurred in elderly, female, orthopedic patients in whom CNB followed LMWH and 16 had taken other drugs affecting hemostasis. In 1997, Tryba & Wedel compared the European experience (once daily regimens and practice guidelines) with the American, and estimated the comparative incidence at 1 in 2,250,000 versus 1 in 14,000.[28]

By April 1998 reports in the USA had increased to 40, of which at least 23 involved epidural catheters and 6 spinal blocks.[29] Further cases involved concurrent antiplatelet drugs. In Europe, there have been 11 cases to 1998 and in Australia 5 (dalteparin or enoxaparin) to August 1999. An obvious difference in practice was the twice-daily dosage regimen (30 mg enoxaparin bd) approved in the USA compared with 20-40 mg daily in other countries. The former regimen may eliminate the trough in activity most suitable for safe CNB or catheter removal, and subsequently in 1998 the USA approved a 40 mg daily regimen for high risk patients.

These events have prompted several recent reviews, editorials and recommendations.

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