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Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy

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Editor's key points

- The incidence of neuraxial bleeding increases with age, female sex, underlying coagulopathy, difficult placement, and indwelling catheter.
- Patient factors cause variable responses to anticoagulants, requiring close monitoring when inserting and removing catheters.
- Non-steroidal anti-inflammatory drugs alone do not increase risk of haematoma.

The actual incidence of neurological dysfunction resulting from haemorrhagic complications associated with neuraxial block is unknown. Although the incidence cited in the literature is estimated to be <1 in 150 000 epidural and <1 in 220 000 spinal anaesthetics, recent surveys suggest that the frequency is increasing and may be as high as 1 in 3000 in some patient populations. Overall, the risk of clinically significant bleeding increases with age, 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 unfractionated heparin or low molecular weight heparin). The decision to perform spinal or epidural anaesthesia/analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy is made on an individual basis, weighing the small, although definite risk of spinal haematoma with the benefits of regional anaesthesia for a specific patient. 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 neuraxial catheterization. Indwelling catheters should not be removed in the presence of therapeutic anticoagulation, as this appears to significantly increase the risk of spinal haematoma. Vigilance in monitoring is critical to allow early evaluation of neurological dysfunction and prompt intervention. An understanding of the complexity of this issue is essential to patient management.

Keywords: blood, anticoagulants; complications, haemorrhage; epidural; spinal

The actual incidence of neurological dysfunction resulting from haemorrhagic complications associated with neuraxial block is unknown. The incidence cited in the literature is estimated to be <1 in 150 000 epidurals and <1 in 220 000 spinal anaesthetics.[1 2] A review of the literature between 1906 and 1994 reported 61 cases of spinal haematomas associated with epidural or spinal aneasthesia.[3] In 87% of patients, a haemostatic abnormality or traumatic/difficult needle placement was present. More than one risk factor was present in 20 of 61 cases. Importantly, although only 38% of patients had partial or good neurological recovery, spinal cord ischaemia tended to be reversible in patients who underwent laminectomy within 8 h of onset of neurological dysfunction.[4]

The need for prompt diagnosis and intervention in the event of a spinal haematoma was also demonstrated in a recent review of the ASA Closed Claims database, which noted that spinal cord injuries were the leading cause of claims in the 1990s.[5] Spinal haematomas accounted for nearly half of the spinal cord injuries. Risk factors for spinal haematoma included epidural anaesthesia in the presence of i.v. heparin during a vascular surgical or diagnostic procedure. Importantly, the presence of postoperative numbness or weakness was typically attributed to local anaesthetic effect rather than spinal cord ischaemia, which delayed the diagnosis. Patient care was rarely judged to have met standards (1 of 13 cases) and the median payment was very high.[4]

It is impossible to conclusively determine risk factors for the development of spinal haematoma in patients undergoing neuraxial block 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 haematoma), and also identify subgroups of patients with higher or lower risk, enhance risk stratification. An epidemiological study investigated serious neurological complications among 1 260 000 spinal and 450 000 epidural blocks performed in Sweden over a 10 yr period.[6] Among the 33 spinal haematomas, 24 occurred in females, and 25 were associated with an epidural technique. The methodology allowed for calculation of frequency of spinal haematoma 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 3600, $P<0.0001$). Likewise, women undergoing hip fracture surgery under spinal anaesthesia had an increased risk of spinal haematoma (1 in 22 000) compared with all patients undergoing spinal anaesthesia (1 in 480 000).[4]

The majority of spinal haematomas occur in the epidural space because of the prominent venous plexus.[3 6] However, the actual source of the bleeding (arterial or venous) is controversial. Bleeding from an arterial source should accumulate rapidly and cause neural ischaemia soon after vessel trauma. However, most spinal haematomas become symptomatic several days after needle/catheter placement, *not* immediately after operation, suggesting the bleeding is not arterial. On the other hand, a venous source would accumulate more slowly, but theoretically would tamponade before overcoming spinal cord perfusion pressure. Thus, neither model entirely represents the clinical scenario. The volume of blood required to cause cord ischaemia also varies, and is affected by the site of bleeding (the cauda equina is relatively resistant, while the watershed areas of the cord are more easily compromised), the presence of vertebral column abnormalities, and the rapidity in which the blood accumulates. It is interesting to note that several of the haematomas associated with low molecular weight heparin (LMWH) involved less blood than that typically injected during the performance of an epidural blood patch.[7]

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.[8]

Finally, while historically concern regarding regional-anaesthesia-related bleeding focused on neuraxial techniques, recent publication of large series of patients undergoing uneventful peripheral block in combination with antithrombotic therapy and case reports of haemorrhagic complications after peripheral techniques provides sufficient information to allow for evidence-based recommendations.[8]

Guidelines for antithrombotic therapy

In 2008, the American College of Chest Physicians (ACCP) released the proceedings of the Eighth Conference on Antithrombotic and Thrombolytic Therapy[9] (Table 1). These recommendations represent new challenges in the management of patients undergoing neuraxial (and invasive/non-compressible peripheral) block. In general, higher degrees of thromboprophylaxis for extended intervals are recommended. An acceptable alternative to the ACCP guidelines are those developed by the Surgical Care Improvement Project (SCIP; www.qualitynet.org). In addition, it is important to note that in response to ongoing concerns regarding surgical bleeding associated with thromboprophylaxis, the American Academy of Orthopaedic Surgeons (AAOS) also published guidelines in 2007 for the prevention of symptomatic pulmonary embolism (rather than deep venous thrombosis) in patients undergoing total joint replacement (www.aaos.org/guidelines.pdf). In general, the AAOS guidelines are more conservative and recommend routine mechanical prophylaxis and aggressive chemoprophylaxis for higher risk patients only.[8]

Table 1 Levels of thromboembolism risk and recommended thromboprophylaxis in hospital patients (Section 1.3). *Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis. †Mechanical thromboprophylaxis includes intermittent pneumatic compression, venous foot pump, and/or graduated compression stockings: consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases. LMWH, low molecular weight heparin; LDUH, low dose unfractionated heparin; INR, international normalized ratio. From Geerts and colleagues[9]

Levels of risk	Approximate DVT risk without thromboprophylaxis (%)*	Suggested thromboprophylaxis options
Low risk	<10	
Minor surgery in mobile patients		No specific thromboprophylaxis
Medical patients who are fully mobile		Early and 'aggressive' ambulation
Moderate risk	10–40	
Most general, open gynaecological or urological surgery patients		LMWH (at recommended doses), LDUH bid or tid, fondaparinux
Medical patients, bed rest, or sick		
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis†
High risk	40–80	
Hip or knee arthroplasty, hip fracture surgery		LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2–3)
Major trauma, spinal cord injury		
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis†

An understanding of the mechanisms of blood coagulation, the pharmacological properties of the anticoagulant and antiplatelet medications, and also the clinical studies involving patients undergoing central neural block while receiving these medications is paramount in reducing the risk of spinal haematoma in patients undergoing neuraxial block[10] (Table 2).

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) 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. Haemostasis remains altered for ~1 day after administration of a thrombolytic drug. Fibrinogen is the last factor to recover.[4]

In addition to the fibrinolytic agent, these patients frequently receive i.v. heparin to maintain an activated partial thromboplastin time (aPTT) of 1.5–2 times normal and clopidogrel/aspirin. No controlled studies have examined the risk. Several of the reported cases of spinal haematoma in patients with indwelling epidural catheters who received thrombolytic agents have been reported in the literature and through the MedWatch system.[4]

Guidelines detailing original contraindications for thrombolytic drugs suggest avoidance of these drugs within 10 days of puncture of non-compressible vessels. Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.[4]

Regional anaesthetic management of the patient on thrombolytic and fibrinolytic therapy[11]

- Patients receiving fibrinolytic and thrombolytic drugs should be cautioned against receiving spinal or epidural anaesthetics except in highly unusual circumstances.
- There is no definitive recommendation for timing of neuraxial catheter removal in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. The measurement of fibrinogen might be helpful to assess the presence of residual thrombolytic effects.

Oral anticoagulants

Patients react with different sensitivities to anticoagulants. Highly sensitive patients exhibit a greater increase in the degree of anticoagulation and prolonged effect after discontinuation of the medication. A single dose (3–5 mg) of warfarin resulted in prolongation of the prothrombin time (PT) in ~20% of patients.[12] Conversely, in resistant patients, the anticoagulant effects are decreased and short-lived. A number of factors affect a patient's sensitivity to heparin and warfarin, including overall medical condition, diet, renal function, and liver disease (Table 3).

Anaesthetic management of patients anticoagulated perioperatively with warfarin depends on dosage and timing of initiation of therapy. The PT and international normalized ratio (INR) of patients on chronic oral anticoagulation requires 3–5 days to normalize after discontinuation of the anticoagulant therapy.[13] Theoretically, since the PT and INR reflect predominantly factor VII activity (and factor VII has only a 6–8 h half-life), there might be an interval during which the PT and INR approach normal values, yet factors II and X levels are not be adequate for haemostasis. Adequate levels of *all* vitamin K-

Table 2 Pharmacological activities of anticoagulants, antiplatelet agents, and thrombolytics. PT, prothrombin time; aPTT, activated partial thromboplastin time; ↑, clinically insignificant increase; ↑↑, possibly clinically significant increase; ↑↑↑, clinically significant increase; NSAID, non-steroidal anti-inflammatory drug. Adapted from Horlocker and Wedel.[10] With permission

Agent	Effect on coagulation variables		Time to peak effect	Time to normal haemostasis after discontinuation
	PT	APTT		
I.V. heparin	↑	↑↑↑	Minutes	4–6 h
Subcutaneous heparin	—	↑	40–50 min	4–6 h
Low molecular weight heparin	—	—	3–5 h	12–24 h
Warfarin	↑↑↑	↑	4–6 days (Less with loading dose)	4–6 days
Dabigatran	↑	↑↑	2 h	4–7 days
Antiplatelet agents				
Aspirin	—	—	Hours	5–8 days
Other NSAIDs			Hours	1–3 days
Ticlopidine, clopidogrel, prasugrel			Hours	5–14 days
Platelet glycoprotein IIb/IIIa receptor inhibitors			Minutes	8–48 h
Fibrinolytics	↑	↑↑	Minutes	24–36 h

Table 3 Summary of patient characteristics associated with enhanced PT response to warfarin

- Age >65 yr
- Female gender
- Weight <100 lb
- Excessive surgical blood loss
- Liver, cardiac, renal disease
- Oriental race
- CYP2C9, VKORC1 genetic variation, or both

dependent factors are typically present when the INR is in the normal range. Therefore, it is recommended that documentation of normal coagulation status be achieved before implementation of neuraxial block.[8] Patients who have only recently normalized their PT/INR after discontinuation of warfarin can have an accelerated response to postoperative warfarin therapy because of residual (subclinical) effect.[4]

Upon initiation of warfarin therapy, the effects are not apparent until a significant amount of biologically inactive factors are synthesized and endogenous factor activity has decayed dependent on factor half-life:

Factor	Half-life (h)
Factor VII	6–8
Factor IX	24
Factor X	25–60
Factor II	50–80

An understanding of the correlation between the various vitamin K-dependent factor levels and the INR is critical to regional anaesthetic management. Clinical experience with patients who are congenitally 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 haemostasis. Bleeding may occur if the level of any clotting factor is decreased to 20–40% of baseline. The PT and INR are most sensitive to the activities of factors VII and X and are relatively insensitive to factor II. Since factor VII has a relatively short half-life, prolongation of the PT and INR can occur in 24–36 h. Prolongation of the INR (INR>1.2) occurs when factor VII activity is reduced to ~55% of baseline, while an INR=1.5 is associated with a factor VII activity of 40%. Thus, an INR<1.5 should be associated with normal haemostasis.[4] A recent analysis of factor VII activity levels and PT/INR supported this, but also reported that patients with prolonged PT/INR can have factor VII activity levels that range from normal to markedly decreased. This suggests that a normal PT/INR is reassuring for neuraxial catheterization, but interpretation of a *prolonged* PT/INR and factor VII activity is difficult and might result in early (and unnecessary) removal of an epidural in ~10% of patients.[14]

Management of patients receiving warfarin is based on the pharmacology of the drug, the levels of vitamin-K-dependent factors required for adequate haemostasis in the surgical setting, and the cases of reported spinal haematoma.[8] The optimal duration of an indwelling catheter and the timing of its removal remain controversial. To date, four studies, with a combined total of nearly 6000 patients, have evaluated the risk of spinal haematoma in patients with indwelling spinal or epidural catheters who receive oral anticoagulants perioperatively.[15–18] These investigations noted that patients respond with great variability to warfarin. Although the mean PT might not increase outside the normal range until 48 h after initiation of therapy, a substantial number of patients will have prolongation after a single dose. Larger doses (greater than warfarin 5 mg) can exaggerate these findings. As a result, it is important to monitor the PT daily to avoid excessive prolongation.[8]

Regional anaesthetic management of the patient on oral anticoagulants[11]

- Discontinue oral anticoagulation and verify PT normalization before neuraxial block.
- Monitor the PT and INR daily.
- Remove indwelling neuraxial catheters when the INR is <1.5 in order to assure that adequate levels of all vitamin-K-dependent factors are present.
- There is no definitive recommendation for facilitating removal of neuraxial catheters in patients with INR >1.5 but <3.0. Removal of neuraxial catheters should be done with caution and neurological status assessed until the INR has been stabilized.
- In patients with an INR>3, warfarin should be withheld. No definitive recommendation can be made regarding the management to facilitate removal of neuraxial catheters (e.g. partial or complete reversal of anticoagulant effect, or discontinuation of warfarin therapy with spontaneous recovery of haemostasis). Individual factor levels might be helpful.

I.V. and subcutaneous standard (unfractionated) heparin

Complete systemic heparinization to attain an aPTT twice baseline is usually reserved for the most high-risk patients, typically patients with acute thromboembolism. However, intraoperative administration of a modest i.v. dose (~5000 units) is frequently performed during vascular procedures. A study involving more than 4000 patients demonstrated the safety of indwelling spinal and epidural catheters during systemic heparinization.[19] 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 neurological literature[20] reported spinal haematomas in seven of 342 patients (2%) who underwent a diagnostic lumbar

puncture and subsequent heparinization. Traumatic needle placement and initiation of anticoagulation within 1 h of lumbar puncture or concomitant aspirin therapy were identified as risk factors in the development of spinal haematoma in anticoagulated patients. Overall, large published series and extensive clinical experience suggest that 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 haematoma in the ASA Closed Claims database suggest that these events might not be as rare as suspected and that extreme vigilance is necessary to diagnose and intervene as early as possible, should spinal haematoma be suspected.[8 21]

The use of epidural and spinal anaesthesia and analgesia in the presence of high-dose intraoperative systemic heparin, specifically in cardiac surgery, has gained recent popularity. A survey of the membership of the Society of Cardiovascular Anesthesiologists surveyed 3974 cardiac anaesthesiologists, and found 7% of their responders used spinal or epidural techniques for cardiac surgery.[22] Interestingly, the majority of anaesthesiologists would proceed if frank blood was noted in the spinal or epidural needle. To date there are no case reports of spinal haematomas associated with this technique published or within the Closed Claims Project.[21] The risk of haematoma among these patients has been estimated. Using a complex mathematical analysis of the probability of predicting a rare event that has not occurred yet, the probability of an epidural haematoma (based on the totals of 4583 epidural and 10 840 spinal anaesthetics reported without complications) to be in the neighbourhood of 1:1528 for epidural and 1:3610 for spinal technique.[4 23]

Low-dose subcutaneous unfractionated heparin is administered for thromboprophylaxis in patients undergoing major thoracoabdominal surgery and also in patients at increased risk of haemorrhage with oral anticoagulant or LMWH therapy. Subcutaneous heparin does not provide adequate prophylaxis after major orthopaedic surgery, and is seldom utilized in this patient population. A review of the literature noted no spinal haematomas in more than 9000 patients who received subcutaneous heparin in combination with spinal or epidural anaesthesia.[24] There are only four cases of spinal haematoma associated with neuraxial block in the presence of low-dose heparin, three of which involved a continuous epidural anaesthetic technique.[3 4] It is important to note that while the ACCP guidelines are more often recommending thrice daily dosing of subcutaneous heparin (due to patient co-morbidities and increased risk of thromboembolism), the safety of neuraxial block in these patients is unknown[9] (Table 2).

Regional anaesthetic management of the patient receiving unfractionated heparin[11]

- Regional anaesthesia and i.v. heparinization for patients undergoing vascular surgery is acceptable with the following recommendations:
  - Delay i.v. heparin administration for 1 h after needle/catheter placement.
  - Prolonged anticoagulation appears to increase risk of spinal haematoma formation, especially if combined with other anticoagulants or thrombolytics. If systematic anticoagulation therapy is begun with an epidural catheter in place, delay catheter removal for 2–4 h after heparin discontinuation and after evaluation of coagulation status.
  - Remove indwelling catheters 1 h before a subsequent heparin administration.
- There is no contradiction to the use of neuraxial techniques during subcutaneous standard heparin at total doses $<10\,000$ units daily. The risk of spinal haematoma with larger daily subcutaneous doses is unclear; assess on an individual basis and implement more frequent neurological monitoring.
- Serial platelet counts are indicated for patients receiving subcutaneous heparin for >5 days.

Low molecular weight heparin

Enoxaparin, the first LMWH to be approved by the US Food and Drug Administration (FDA), was distributed for general use in May 1993. Within 1 yr, two cases of spinal haematoma had been voluntarily reported through the MedWatch system. Despite repeated efforts at relabelling and education, cases of spinal haematoma continued to occur. A total of 30 cases of spinal haematoma in patients undergoing spinal or epidural anaesthesia while receiving LMWH perioperatively were reported between May 1993 and November 1997. A Health Advisory was issued by the FDA in December 1997. In addition, the manufacturers of all LMWH and heparinoids were requested to place a 'boxed warning'.[4]

At the time of the Consensus Conference on Neuraxial Anaesthesia and Anticoagulation in April 1998, there were 45 cases of spinal haematoma associated with LMWH, 40 involved a neuraxial anaesthetic. 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 neurological dysfunction was 3 days, while median time to onset of symptoms and laminectomy was more than 24 h. Less than one-third of the patients reported fair or good neurological recovery.[4 7]

The risk of spinal haematoma, based on LMWH sales, prevalence of neuraxial techniques, and reported cases, was estimated to be $\sim$1 in 3000 continuous epidural anaesthetics compared with 1 in 40 000 spinal anaesthetics.[25] However, this is most likely an underestimation; in addition to the spinal haematomas that had been reported at the time of the First Consensus Conference, there were $\sim$20 more that had occurred, but were not yet reported to the MedWatch system. In total, nearly 60 spinal haematomas were tallied by the FDA between 1993 and 1998.[4]

There were only 13 cases of spinal haematoma after neuraxial block between 1998 and 2002 (the timing of the second

Table 4 Patient, anaesthetic, and LMWH dosing variables associated with spinal haematoma. LMWH, low molecular weight heparin. From Horlocker and colleagues.[4] With permission

Patient factors
Female gender
Increased age
Ankylosing spondylitis or spinal stenosis
Renal insufficiency
Anaesthetic factors
Traumatic needle/catheter placement
Epidural (compared with 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

Consensus Conference) reported through the MedWatch system or published as case reports.[4] In addition to LMWH, five patients received ketorolac, one patient received ibuprofen, and one patient received i.v. unfractionated heparin during a vascular procedure. The regional technique was a spinal anaesthetic in three cases. The remaining 10 patients underwent epidural anaesthesia in combination with LMWH therapy. Thus, the characteristics of the reported cases support the previous recommendations of epidural catheter removal before the initiation of LMWH thromboprophylaxis and avoidance of concomitant antiplatelet/anticoagulant medications[4] (Table 4). The impact of renal function was also likely to be underestimated. In patients with severe renal insufficiency, the anticoagulant effect is exaggerated and the elimination half live prolonged from 4–6 h to as long as 16 h.[26]

The indications and labelled uses for LMWH continue to evolve. Indications for thromboprophylaxis and treatment of deep venous thrombosis (DVT)/pulmonary embolism (PE) or myocardial infarction have been introduced since the first Consensus Conference. These new applications and corresponding regional anaesthetic management warrant discussion.[9] Several off-label applications of LMWH are of special interest to the anaesthesiologist. 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 h after this level of LMWH anticoagulation.[4]

Regional anaesthetic management of the patient receiving low molecular weight heparin[11]

Perioperative management of patients receiving LMWH requires coordination and communication. It is also important to note that even when protocols for dosing of LMWH and catheter management exist, they might not be closely followed.[27] In one series, the authors reported a 52% non-compliance 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. Concomitant antiplatelet or oral anticoagulant medications administered in combination with LMWH is not recommended.

Preoperative LMWH

- Perform neuraxial techniques at least 10–12 h after a thromboprophylaxis dose and 24 h after a high therapeutic dose of LMWH.

Postoperative LMWH

- With twice daily dosing, administer the first dose of LMWH no earlier than 24 h after operation, regardless of anaesthetic technique, and only in the presence of adequate haemostasis.
  - Remove indwelling catheters before initiation of LMWH thromboprophylaxis.
  - The first dose of LMWH administered 2 h after catheter removal and 24 h after needle/catheter placement, whichever is later.
- Once daily dosing requires 6–8 h between needle/catheter placement and the first dose of LMWH. Subsequent dosing should occur no sooner than 24 h later.

Antiplatelet medications

Antiplatelet medications, including non-steroidal anti-inflammatory drugs (NSAIDs), thienopyridines, and glycoprotein IIb/IIIa inhibitors, are seldom used as primary agents of thromboprophylaxis. Many orthopaedic patients report chronic use of one or more NSAIDs, including aspirin, ibuprophen, ketorolac, and naproxen.[28] Although antiplatelet therapy was implicated in three of the 61 cases of spinal haematoma occurring after spinal or epidural anaesthesia,[3] several large studies have demonstrated the relative safety of neuraxial block in both obstetric, surgical, and pain clinic patients receiving these medications.[8 28–30] A prospective study involving 1000 patients 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.[28] The clinician should be aware of the possible increased risk of spinal haematoma in patients receiving antiplatelet medications who undergo subsequent heparinization.[20] Ticlopidine and clopidogrel, as thienopyridines, are also platelet aggregation inhibitors. These agents interfere with platelet–fibrinogen binding and subsequent platelet–platelet interactions.[4] The effect is irreversible for the life of the platelet. Ticlopidine and clopidogrel have no effect on platelet cyclooxygenase, acting independently of

aspirin. Platelet dysfunction is present for 5–7 days after discontinuation of clopidogrel and 10–14 days with ticlopidine. Completely normal clotting is not required for safe block, hence the range for clopidogrel. Prasugrel is a new thienopyridine which inhibits platelets more rapidly, more consistently, and to a greater extent than do standard and higher doses of clopidogrel. In the USA, the only labelled indication is for acute coronary syndrome in patients intended to undergo percutaneous coronary intervention. After a single oral dose, 50% of platelets are irreversibly inhibited, with maximum effect 2 h after administration. Platelet aggregation normalizes in 7–9 days after discontinuation of therapy. The labelling recommends that the drug 'be discontinued at least 7 days before any surgery'.

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 after discontinuation of therapy ranges from 8 h (eptifibatide, tirofiban) to 48 h (abciximab).[4] Increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine and clopidogrel warrants concern regarding the risk of anaesthesia-related haemorrhagic complications.[31]

Regional anaesthetic management of the patient receiving antiplatelet medications[11]

- The concurrent use of medications that affect other components of clotting mechanisms, such as oral anticoagulants, standard heparin, and LMWH, increases the risk of bleeding complications for patients receiving antiplatelet agents.
- NSAIDs, by themselves, represent no significant risk for the development of spinal haematoma in patients having epidural or spinal anaesthesia.
- Allow platelet function to recover before neuraxial block after administration of ticlopidine, clopidogrel, and platelet GP IIb/IIIa receptor antagonists. The time to normal platelet aggregation after discontinuation of therapy is 14 days for ticlopidine, 5–7 days for clopidogrel, and 7–10 days for prasugrel. For the platelet GP IIb/IIIa inhibitors, the duration ranges from 8 h for eptifibatide and tirofiban to 48 h after abciximab administration.

Herbal medications

There is a widespread use of herbal medications in surgical patients. Morbidity and mortality associated with herb use might 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 current regulatory mechanisms for commercial herbal preparations do not adequately protect against unpredictable or undesirable pharmacological effects, it is especially important for anaesthesiologists to be familiar with related literature on herbal medications when caring for patients in the perioperative period.[4 32]

Regional anaesthetic management of the patient receiving herbal therapy[11]

- Herbal drugs, by themselves, appear to represent no added significant risk for the development of spinal haematoma in patients having epidural or spinal anaesthesia. This is an important observation since it is likely that a significant number of surgical patients utilize alternative medications before operation and perhaps during their postoperative course. There is no wholly accepted test to assess adequacy of haemostasis 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 might increase the risk of bleeding complications in these patients.

Fondaparinux

Fondaparinux (Arixtra®), a synthetic pentasaccharide, was approved by the FDA in December 2001 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 h, allowing for single daily dosing, with the first dose administered 6 h after operation. Investigators reported a spinal haematoma among the initial dose-ranging study (at a dose that was subsequently determined to be twice that required for thromboprophylaxis).[33 34] No additional spinal haematomas were reported in the combined series of 3600 patients who underwent spinal or epidural anaesthesia 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 h before fondaparinux administration.[34] These practice guidelines might not be feasible in clinical practice. For example, in a prospective series, $<$40% of neuraxial blocks were successful with one pass.[4 28] A recent series of 1631 patients undergoing continuous neuraxial or deep peripheral block reported no serious haemorrhagic complications. However, the catheters were removed 36 h after the last dose of fondaparinux and subsequent dosing was delayed for 12 h after catheter removal.[35] While these results are reassuring, the deviation from the manufacturer's suggested dosing guidelines is of concern. Although the actual risk of spinal haematoma with fondaparinux is unknown, extreme caution is warranted, given the sustained antithrombotic effect, early postoperative dosing, and 'irreversibility'.[8]

Regional anaesthetic management of the patient receiving fondaparinux[11]

- Until additional clinical information is obtained, neuraxial techniques should be performed and managed 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.

Dabigatran

Dabigatran etexilate is a prodrug that specifically and reversibly inhibits both free and clot-bound thrombin. The prodrug is absorbed from the gastrointestinal tract with a bioavailability of 5%.[36] Once absorbed, it is converted by esterases into its active metabolite, dabigatran. Plasma levels peak at 2 h. The half-life is 8 h after a single dose and up to 17 h after multiple doses. It is likely that once daily dosing will be possible for some indications because of the prolonged half-life. Because 80% of the drug is excreted unchanged by the kidneys, it is contraindicated in patients with renal failure.[37] Dabigatran prolongs the aPTT, but its effect is not linear and reaches a plateau at higher doses. However, the ecarin clotting time (ECT) and thrombin time (TT) are particularly sensitive and display a linear dose–response at therapeutic concentrations. Reversal of anticoagulant effect is theoretically possible through administration of recombinant factor VIIa, although this has not been attempted clinically.[37] Indeed, product labelling suggests that dialysis be considered for patients with significant bleeding due to dabigatran.[8]

Clinical trials comparing dabigatran (150 or 220 mg, with the first dose administered 1–4 h after operation) with enoxaparin (40 mg daily with first dose 12 h before operation) noted little difference in efficacy or bleeding.[38–40] Among published series, there has been no attempt to randomize patients with respect to anaesthetic technique, nor impose exclusion criteria based on the performance of neuraxial block, including the presence of an indwelling epidural catheter or traumatic needle/catheter placement.[38–40] While there have been no reported spinal haematomas, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach.[8] Currently, the only labelled indication is for patients with non-valvular atrial fibrillation. Fortunately, suspension of anticoagulation therapy in these patients does not place them at significant risk of thromboembolism. Thus, an early discontinuation to allow complete resolution of drug effect (5–7 days, depending on renal function) in anticipation of surgery and delayed resumption of dabigatran after operation is reasonable.

Regional anaesthetic management of the patient receiving dabigatran

- Given the irreversibility of dabigtran, the prolonged half-life, and the uncertainty of an individual patient's renal function, dabigatran should be discontinued 7 days before neuraxial block. If a shorter time interval is desired, reversal of anticoagulant effect should be documented by assessment of TT or ECT. Neuraxial catheters should be removed at least 6 h before initiation of dabigatran therapy.[26]

Rivaroxaban

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor, with an oral bioavailability of 80%. After administration, the maximum inhibitory effect occurs 1 to 4 hours; however, inhibition is maintained for 12 h. The antithrombotic effect can be monitored with the PT, aPTT, and Heptest, all of which demonstrate linear dose effects. Rivaroxaban is cleared by the kidneys and gut. The terminal elimination half-life is 9 h in healthy volunteers and may be prolonged to 13 h in the elderly due to a decline in renal function (hence a need for dose adjustment in patients with renal insufficiency and contraindicated in patients with severe liver disease).[8]

Rivaroxaban was approved in the USA for thromboprophylaxis after total hip or knee replacement in 2011.[8] Overall, clinical trials comparing rivaroxaban (5–40 mg daily, with the first dose 6–8 h after surgery) with enoxaparin (40 mg, beginning 12 h before surgery) demonstrate similar rates of bleeding and comparable efficacy.[41–43] While a 'regional anaesthetic' was performed in more than half of the patients included in the clinical trials, no information regarding needle placement or catheter management was included. Although there have been no reported spinal haematomas, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach.[8]

Regional anaesthetic management of the patient receiving rivaroxaban

- According to European guidelines, 22–26 h should elapse between discontinuation of rivaroxaban and neuraxial block in patients with normal renal function.[26] Longer intervals are required in patients with renal insufficiency. Indwelling neuraxial catheters are contraindicated due to the 'boxed warning'. Four to six hours are recommended between spinal block and initiation of rivaroxaban therapy after operation.[26]

Peripheral and plexus block

Although spinal haematoma is the most significant haemorrhagic complication of regional anaesthesia due to the catastrophic nature of bleeding into a fixed and non-compressible space, the associated risk after plexus and peripheral techniques remains undefined. There are no investigations that examine the frequency and severity of haemorrhagic complications after plexus or peripheral block in anticoagulated patients. However, few reports of serious complications after neurovascular sheath cannulation for

surgical, radiological, or cardiac indications have been reported. Overall, there have been 26 cases of haemorrhagic complications in patients reported after plexus/peripheral techniques; in 13 cases, the patient had altered haemostasis. The cases of major bleeding were likely to occur after psoas compartment or lumbar sympathetic block and/or in the presence of anticoagulants or antiplatelet agents. Neurological compromise was not always reported.[8 44–46]

These cases suggest that significant blood loss (resulting in transfusion or even death), rather than neural deficits, might be the most serious complication of non-neuraxial regional techniques in the anticoagulated patient. Given the paucity of information, it is impossible to make definitive recommendations. Conservatively, the Consensus Statements on Neuraxial Anaesthesia and Anticoagulation can be applied to plexus and peripheral techniques. However, this may be more restrictive than necessary for techniques involving superficial and compressible vasculature.[4 8]

Anaesthetic management of the patient undergoing plexus or peripheral block[11]

- For patients undergoing deep plexus or deep peripheral block, recommendations regarding neuraxial techniques should be similarly applied.

Diagnosis and treatment of compressive haematoma

The differential diagnosis of new or progressive postoperative neurological symptoms includes surgical neuropraxia, prolonged/exaggerated neuraxial block, anterior spinal artery syndrome, epidural abscess, exacerbation of a preexisting neurological disorder, and presentation of a previously undiagnosed neurological condition, and also spinal haematoma. The onset of symptoms immediately after operation is uncommon; it is rare for a spinal haematoma to present as a 'prolonged' neuraxial block.[3 6 7] The time interval between needle placement/initiation of thromboprophylaxis and neurological dysfunction is typically on the order of days. Once new neurological deficits are noted, complete paralysis develops over 10–15 h.

Evaluation is focused on identification of reversible/treatable causes. Therefore, any new or progressive neurological symptoms occurring in the presence of epidural analgesia warrant immediate discontinuation of the infusion (with the catheter left *in situ*) to rule out any contribution from the local anaesthetic or volume effect. If the epidural is the aetiology of the deficits, a prompt return of function should be noted. Since neurological outcome is linked to early diagnosis and intervention, it is critical to obtain radiographic imaging, preferably magnetic resonance imaging, as soon as possible. Consultation with a neurosurgeon should also occur as soon as possible to determine the urgency of surgery. Interestingly, not all spinal haematomas are treated with emergency laminectomy; spontaneous resolution of deficits has been reported.[3 6 7] However, the decision to observe *vs* surgically intervene is a neurosurgical one. In all series, the neurological outcome is poor for the majority of patients. In addition, it was noted that if more than 8 h was allowed to elapse between the development of paralysis and surgical intervention, complete neurological recovery was unlikely. In general, bleeding after peripheral techniques is of a lesser concern than neuraxial haematoma and often presents as hypovolaemia, rather than neurodeficits. As with neuraxial haematoma, the decision to intervene or observe is based on severity of the bleeding and the presence of neural deficits.

Conclusions

Recognition of the risks associated with spinal and epidural block and anticoagulation, continued surveillance, and evaluation of the current information, and education are all crucial to averting future cases of spinal haematoma. The introduction of new anticoagulants and antiplatelet agents, the complexity of balancing thromboembolic with haemorrhagic complications, and the evolving indications for regional anaesthesia/analgesia necessitate an individualized approach (Table 5). Thus, the decision to perform spinal or epidural anaesthesia/analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, weighing the small, although definite risk of spinal haematoma with the benefits of regional anaesthesia for a specific patient. Alternative anaesthetic 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 (Table 6). Indwelling catheters should not be removed in the

Table 5 Trends in thromboprophylaxis that could increase risk of spinal haematoma

- Thromboprophylaxis (e.g. standard and LMWH for patients undergoing general surgery) is often administered in close proximity to surgery. Unfortunately, early postoperative dosing is associated with surgical (and often anaesthesia-related) bleeding
- Fondaparinux is recommended as an antithrombotic agent after major orthopaedic surgery. The extended half-life (~20 h) impedes safe catheter removal
- Low molecular weight heparin and dabigatran depend on renal metabolism. Dose adjustment for decreased weight, renal function, or both is not performed routinely and could result in an exaggerated and prolonged effect
- The duration of prophylaxis has been extended to include 'post-dismissal' administration. It has been demonstrated that the risk of bleeding complications is increased with the duration of anticoagulant therapy
- Newly released and investigational antithrombotic agents are associated with prolonged half-lives, are not routinely monitored for anticoagulant effect, and do not have pharmacological antidotes

Table 6 Recommendations for management of patients receiving neuraxial block and anticoagulant drugs. NSAIDs, non-steroidal anti-inflammatory drugs; GP IIb/IIIa, platelet glycoprotein receptor IIb/IIIa inhibitors; INR, international normalized ratio; LMWH, low molecular weight heparin; aPTT, activated partial thromboplastin time; TT, thrombin time. Recommendations from Horlocker and colleagues[11]

Warfarin	Discontinue chronic warfarin therapy 4–5 days before spinal procedure and evaluate INR. INR should be within the normal range at the time of procedure to ensure adequate levels of all vitamin K-dependent factors. After operation, daily INR assessment with catheter removal occurring with INR<1.5
Antiplatelet medications	No contraindications with aspirin or other NSAIDs. Thienopyridine derivatives (clopidogrel and prasugrel) should be discontinued clopidogrel 5–7 days, prasugreal 7 days, and ticlopidine 14 days before procedure. GP IIb/IIIa inhibitors should be discontinued to allow recovery of platelet function before procedure (8 h for tirofiban and eptifibatide, 24–48 h for abciximab)
Thrombolytics/ fibrinolytics	There are no available data to suggest a safe interval between procedure and initiation or discontinuation of these medications. Follow fibrinogen level and observe for signs of neural compression
LMWH	Delay procedure at least 12 h from the last dose of thromboprophylaxis LMWH dose. For 'treatment' dosing of LMWH, at least 24 h should elapse before procedure. LMWH should not be administered within 24 h after the procedure. Indwelling epidural catheters should be maintained only with once daily dosing of LMWH and strict avoidance of additional haemostasis altering medications, including NSAIDs
Unfractionated s.c. heparin	There are no contraindications to a neuraxial procedure if total daily dose is <10 000 units. For higher dosing regimens, increase neurological monitoring and cautiously co-administer antiplatelet medications
Unfractionated i.v. heparin	Delay needle/catheter placement 2–4 h after last dose, document normal aPTT. Heparin may be restarted 1 h after procedure. Sustained heparinization with an indwelling neuraxial catheter associated with increased risk; monitor neurological status aggressively
Dabigatran	Discontinue 7 days before procedure; for shorter time periods, document normal TT. First postoperative dose 24 h after needle placement and 6 h post-catheter removal (whichever is later)

presence of therapeutic anticoagulation, as this appears to significantly increase the risk of spinal haematoma. Identification of risk factors and establishment of guidelines will not completely eliminate the complication of spinal haematoma. Vigilance in monitoring is critical to allow early evaluation of neurological dysfunction and prompt intervention. We must focus not only on the prevention of spinal haematoma, but also optimization of neurological outcome.[8]

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References

1 Tryba M. Epidural regional anesthesia and low molecular heparin: Pro. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1993; **28**: 179–81

2 Stafford-Smith M. Impaired haemostasis and regional anaesthesia. *Can J Anaesth* 1996; **43**: R129–41

3 Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal–epidural anesthesia. *Anesth Analg* 1994; **79**: 1165–77

4 Horlocker TT, Wedel DJ, Benzon H, *et al.* Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; **28**: 172–97

5 Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. *Anesth Analg* 1997; **84**: 1211–21

6 Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology* 2004; **101**: 950–9

7 Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing perioperative analgesia and thromboprophylaxis. *Reg Anesth Pain Med* 1998; **23**: 164–77

8 Horlocker TT, Wedel DJ, Rowlingson JC, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35**: 64–101

9 Geerts WH, Bergqvist D, Pineo GF, *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 381S–453S

10 Horlocker TT, Wedel DJ. Anticoagulation and neuraxial block: historical perspective, anesthetic implications, and risk management. *Reg Anesth Pain Med* 1998; **23**: 129–34

11 Horlocker TT, Birnbach DJ, Connis RT, *et al.* Practice advisory for the prevention, diagnosis, and management of infectious complications associated with neuraxial techniques: a report by the American Society of Anesthesiologists Task Force on infectious complications associated with neuraxial techniques. *Anesthesiology* 2010; **112**: 530–45

12 Horlocker TT, Wedel DJ, Schlichting JL. Postoperative epidural analgesia and oral anticoagulant therapy. *Anesth Analg* 1994; **79**: 89–93

13 Heit JA. Perioperative management of the chronically anticoagulated patient. *J Thromb Thrombolysis* 2001; **12**: 81–7

14 Benzon HT, Avram MJ, Benzon HA, Kirby-Nolan M, Nader A. Factor VII levels and international normalized ratios in the early phase of warfarin therapy. *Anesthesiology* 2010; **112**: 298–304

15 Horlocker TT, Cabanela ME, Wedel DJ. Does postoperative epidural analgesia increase the risk of peroneal nerve palsy after total knee arthroplasty? *Anesth Analg* 1994; **79**: 495–500

16 Liu SS, Buvanendran A, Viscusi ER, *et al.* Uncomplicated removal of epidural catheters in 4365 patients with international normalized ratio greater than 1.4 during initiation of warfarin therapy. *Reg Anesth Pain Med* 2011; **36**: 231–5
17 Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. *Anaesthesia* 1983; **38**: 254–9
18 Wu CL, Perkins FM. Oral anticoagulant prophylaxis and epidural catheter removal. *Reg Anesth* 1996; **21**: 517–24
19 Rao TL, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. *Anesthesiology* 1981; **55**: 618–20
20 Ruff RL, Dougherty JH Jr. Complications of lumbar puncture followed by anticoagulation. *Stroke* 1981; **12**: 879–81
21 Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia: a closed claims analysis. *Anesthesiology* 1999; **90**: 1062–9
22 Goldstein S, Dean D, Kim SJ, *et al.* A survey of spinal and epidural techniques in adult cardiac surgery. *J Cardiothorac Vasc Anesth* 2001; **15**: 158–68
23 Ho AM, Chung DC, Joynt GM. Neuraxial blockade and hematoma in cardiac surgery: estimating the risk of a rare adverse event that has not (yet) occurred. *Chest* 2000; **117**: 551–5
24 Liu SS, Mulroy MF. Neuraxial anesthesia and analgesia in the presence of standard heparin. *Reg Anesth Pain Med* 1998; **23**: 157–63
25 Schroeder DR. Statistics: detecting a rare adverse drug reaction using spontaneous reports. *Reg Anesth Pain Med* 1998; **23**: 183–9
26 Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2010; **27**: 999–1015
27 McEvoy MD, Bailey M, Taylor D, Del Schutte H Jr. Noncompliance in the inpatient administration of enoxaparin in conjunction with epidural or spinal anesthesia. *J Arthroplasty* 2000; **15**: 604–7
28 Horlocker TT, Wedel DJ, Schroeder DR, *et al.* Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg* 1995; **80**: 303–9
29 CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet* 1994; **343**: 619–29
30 Horlocker TT, Bajwa ZH, Ashraf Z, *et al.* Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg* 2002; **95**: 1691–7
31 Kovesi T, Royston D. Is there a bleeding problem with platelet-active drugs? *Br J Anaesth* 2002; **88**: 159–63
32 Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery* 1990; **26**: 880–2
33 Landow L. A synthetic pentasaccharide for the prevention of deep-vein thrombosis. *N Engl J Med* 2001; **345**: 291–2
34 Turpie AG, Fisher WD, Bauer KA, *et al.* BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. *J Thromb Haemost* 2005; **3**: 2479–86
35 Singelyn FJ, Verheyen CC, Piovella F, Van Aken HK, Rosencher N. The safety and efficacy of extended thromboprophylaxis with fondaparinux after major orthopedic surgery of the lower limb with or without a neuraxial or deep peripheral nerve catheter: the EXPERT Study. *Anesth Analg* 2007; **105**: 1540–7
36 Weitz JI, Hirsh J, Samama MM. New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 234S–56S
37 Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. *Clin Pharmacokinet* 2009; **48**: 1–22
38 Eriksson BI, Dahl OE, Buller HR, *et al.* A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005; **3**: 103–11
39 Eriksson BI, Dahl OE, Rosencher N, *et al.* Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; **5**: 2178–85
40 Eriksson BI, Dahl OE, Rosencher N, *et al.* Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007; **370**: 949–56
41 Eriksson BI, Borris LC, Dahl OE, *et al.* A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59–7939), for thromboprophylaxis after total hip replacement. *Circulation* 2006; **114**: 2374–81
42 Fisher WD, Eriksson BI, Bauer KA, *et al.* Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. *Thromb Haemost* 2007; **97**: 931–7
43 Lassen MR, Ageno W, Borris LC, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; **358**: 2776–86
44 Klein SM, D'Ercole F, Greengrass RA, Warner DS. Enoxaparin associated with psoas hematoma and lumbar plexopathy after lumbar plexus block. *Anesthesiology* 1997; **87**: 1576–9
45 Maier C, Gleim M, Weiss T, Stachetzki U, Nicolas V, Zenz M. Severe bleeding following lumbar sympathetic blockade in two patients under medication with irreversible platelet aggregation inhibitors. *Anesthesiology* 2002; **97**: 740–3
46 Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. *Anesthesiology* 2003; **98**: 581–5