REVIEW ARTICLE
Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies

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Summary
We propose recommendations to reduce the risk of haemorrhagic events associated with regional anaesthesia in patients treated with newer anticoagulants after orthopaedic surgery. The risk/benefit ratio should be individualised for each patient according to the type and dose of anticoagulant, the type of regional anaesthesia and patient risk factors. Neuraxial anaesthetic management strategy can be based on the pharmacokinetic properties of specific anticoagulants, including the time required to reach maximal concentration, half-life, and dose regimen. Central neuraxial blocks should not be performed and epidural catheters should not be removed until at least two half-lives after the last injection of anticoagulant, the half-life depending on renal function. After removing a catheter or after a haemorrhagic puncture, the timing of the next anticoagulant injection should be based on the time required for an anticoagulant dose to reach maximum activity. Vigilance remains paramount during the initial days after removal of a neuraxial catheter.

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Peri-operative thrombotic complications are common; for example, roughly half of all patients not given thromboprophylaxis will develop venographically evident deep-vein thrombosis after major orthopaedic surgery, and 10% of those who do, will suffer a pulmonary embolism [1]. It is thus usual to provide antithrombotic drugs to patients undergoing major orthopaedic surgery [1].

Neuraxial anaesthesia, especially spinal and epidural anaesthesia, is often used for hip and knee arthroplasty, as well as for open reduction and internal fixation of hip fractures. Neuraxial anaesthesia is associated with a small but distinct risk of epidural haematoma (1 haematoma per 150 000 cases) [2]; however, the risk is increased 15-fold by concomitant use of anticoagulant therapy when appropriate precautions are not taken [3]. Haematomas can also be problematic after deep lumbar plexus blocks. Epidural haematomas can be devastating complications, with paralysis occurring even after surgical decompression.

Whatever the anticoagulant agent, the balance between the benefits (prevention of venous thromboembolism, a major cause of peri-operative morbidity and mortality) and risks (major bleeding and epidural haematoma) is the central consideration. This balance not only depends on the pharmacology of each agent, but also on the dosage, timing of administration, the type of surgery and patient characteristics.

Because the incidence of epidural haematoma is so low, it is difficult to study enough patients to determine the specific risk associated with each new antithrombotic agent. For similar reasons, it is impossible to determine accurately how best to minimise the risk of spinal haematoma while maintaining effective prevention of thrombosis. Available guidelines thus aim to minimise the risk of spinal haematoma by restricting catheter or needle insertion and removal to periods when the concentration of anticoagulant is low. Risk can be further reduced by delaying anticoagulation until after surgery – an approach...
which apparently does not increase the risk of venous thrombosis [4, 5].

This brief review will focus on the management of anticoagulant drugs in patients requiring regional anaesthesia. An electronic search was performed using three electronic databases: Pubmed® (MEDLINE/Index Medicus), the Cochrane Central Register of Randomised Controlled Trials published by the Cochrane Library, and Embase. The medical subject heading terms used for the search were ‘neuraxial anaesthesia’, ‘antithrombotic agents’ and ‘orthopaedic surgery’. The electronic research was completed by a manual search in the reference lists of original published articles, reviews and correspondences. We will discuss the relative risks and benefits of regional and general anaesthesia, consider factors that increase the risk of epidural haematomas, and recommend strategies for using neuraxial anaesthesia in patients who are given some of the newer anticoagulants. These recommendations will generally be based on the pharmacology of each anticoagulant.

Overall, anaesthetists should take into consideration the pharmacokinetics of any particular anticoagulants and be alert to the signs and symptoms of epidural haematoma, which include back pain, sensory changes, progressive paralysis and incontinence. Suspicion should prompt diagnostic imaging and, when appropriate, surgical intervention.

**General vs regional anaesthesia for orthopaedic surgery**

Initial studies suggested that the risk of mortality and morbidity (including venous thromboembolism) was less with neuraxial anaesthesia than with general anaesthesia [6–8]. However, one meta-analysis and two large studies failed to confirm this benefit [9–11]. More recently, two meta-analyses by Rodgers et al. [12] and Urwin et al. [13] identified a small decrease of the incidence of deep-vein thrombosis after regional anaesthesia compared with general anaesthesia. A critical point, though, is that both recent meta-analysis included older trials (more than two-thirds were performed before 1990), when thromboprophylaxis was not used routinely for hip fracture surgery.

In most recent studies, using newer anticoagulants and risk-adjusted dosing, the risk of deep-vein thrombosis incidence was not reduced by neuraxial anaesthesia [14]. Available data thus suggest that neuraxial anaesthesia decreased the rate of deep-vein thrombosis before the widespread use of effective prophylactic anticoagulation, but no longer does in patients given appropriate antithrombotic treatment with newer agents [14, 15]. Neuraxial anaesthesia also fails to reduce blood loss or transfusion requirements [16]. Nonetheless, neuraxial anaesthesia is often chosen for elective orthopaedic surgery in preference to general anaesthesia because it provides better pain control and facilitates rehabilitation [17].

**Risk of deep haematoma**

The interval between initiation of low molecular weight heparin (LMWH, e.g. enoxaparin) therapy and neurological dysfunction as a sign of neuraxial haematoma ranges from 15 h to 3 days, but neuraxial haematoma is uncommon immediately after surgery [18, 19]. One explanation for this important lag between puncture or catheter removal and haematoma is the accumulation of anticoagulant after 3 days in older patients with poor creatinine clearance, as an example of patient factors that interplay to influence drug effect. Neurological examinations should thus continue for up to 3 postoperative days as complete neurological recovery is more likely if surgical decompression occurs within 8 h after onset of paralysis [18]. The actual source of the bleeding (arterial or venous) remains controversial and it is difficult to understand why several of the haematomas associated with LMWH involved less blood than the volume routinely injected when performing a therapeutic blood patch [19], a routine treatment for postspinal headache.

Procedure-related risk factors for spinal haematoma include haemorrhagic puncture [20], multiple punctures, catheter insertion and traumatic catheter removal. Formation of spinal haematoma is also facilitated when haemostasis is impaired, for example by the concomitant administration of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or other antiplatelet agents. Additional risk factors for spinal haematoma include older age (> 75 years), female gender, and the presence of spinal column abnormalities [2, 19, 21].

The overall risk of epidural haematoma is estimated to be less than 1 in 150 000 epidural injections and 1 in 220 000 spinal injections [2, 22]. However, this risk increases to 1 in 70 000 and 1 in 150 000, respectively, in patients who had experienced a traumatic spinal tap or were already receiving heparin or acetylsalicylic acid [2]. A recent study by Moen et al. [23] of 1710 000 patients found that the overall incidence of epidural haematomas was around 1 in 50 000 patients, but that the incidence of haematomas increased to 1 in 3600 when analysis was restricted to epidural anaesthesia with a catheter for total knee replacement in women older than 70 years of age. These results are in accordance with those reported in a recent retrospective review [24]. Indeed, three neuraxial haematomas were detected in 8000 neuraxial anaesthetics, always associated with...
epidural catheter, 2 days after insertion of an epidural catheter. Schroeder estimated that the incidence of spinal haematoma in patients undergoing neuraxial blockade in combination with LMWH in the United States was 1 in 40 800 spinal and 1 in 3100 epidural injections [3]. It is thus apparent that risk increases substantially in elderly women in whom an epidural catheter is inserted with concomitant anticoagulant therapy and bloody puncture [20].

**General strategies for use of neuraxial anaesthesia in anticoagulated patients**

It would be difficult to evaluate the risk of spinal haematoma based on data from phase II and III clinical trials of new agents. For one thing, patients with important risk factors for bleeding are typically not included; for another, few if any trials include a sufficient number of patients to quantify this rare event.

**Current recommendations**

Numerous anaesthesia societies, including the American Society of Regional Anesthesia [21] and European groups [25–27], have proposed guidelines to improve the safety of neuraxial techniques performed in patients treated with heparins (unfractionated or low-molecular-weight heparin) or oral anticoagulants (e.g. vitamin K antagonists). These practical recommendations were designed to optimise both the safety and the efficacy of prophylaxis in the presence of neuraxial anaesthesia.

Interestingly, the recommendations for prevention of haemorrhagic complications associated with neuraxial anaesthesia in patients given LMWH differ from country-to-country, and across continents. Indeed, in most European countries, the recommendations are that placement or removal of a spinal or epidural needle/catheter should be delayed at least 12 h after the last anticoagulant dose, but the recommendation is to delay 20 h in France and 10 h in the United States. Subsequent administration of LMWH is not recommended until 4 h after catheter removal in Europe, but is considered acceptable after only 2 h in the USA. In France, LMWH therapy is not initiated until 6 h after surgery in patients having neuraxial anaesthesia [28].

**Considerations for managing epidural catheters in the setting of anticoagulation**

The recommendations we propose are drug-specific and are based on the pharmacokinetics of each agent; specifically, the half-life and time to reach maximum plasma concentration or maximum antithrombotic activity ($T_{\text{max}}$, Table 1). There are two parts to our recommendations: the first is how long to delay before removing neuraxial catheters and the second is when to restart anticoagulation. These recommendations are relevant to doses used for thrombosis prophylaxis, rather than therapeutic anticoagulation.

**Catheter removal**

We suggest delaying removal of a neuraxial catheter until at least two half-lives have elapsed for the specific anticoagulant involved (Figs 1 and 2). After two half-lives, only 25% of the medication remains active. After this interval, elimination slows considerably so waiting longer only slightly decreases the residual drug concentration. An obvious limitation to this strategy is the slight residual anticoagulant activity, but it seems a reasonable compromise between the risk of haemorrhagic complications and the risk of thrombosis.

### Table 1 Pharmacokinetics of anticoagulants in patients with normal creatinine clearance.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half-life; h</th>
<th>$T_{\text{max}}$; h</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH IV [38]</td>
<td>1–2</td>
<td>Immediately</td>
</tr>
<tr>
<td>UFH SC [38]</td>
<td>8–12</td>
<td>2–2.5</td>
</tr>
<tr>
<td>LMWH SC [38]</td>
<td>4–7</td>
<td>3–4</td>
</tr>
<tr>
<td>Fondaparinux SC [32]</td>
<td>17–20</td>
<td>1–2</td>
</tr>
<tr>
<td>Dabigatran (oral) [34]</td>
<td>14–17</td>
<td>2–4</td>
</tr>
<tr>
<td>Rivaroxaban (oral) [23,36,39]</td>
<td>7–9</td>
<td>2–4</td>
</tr>
</tbody>
</table>

UFH, unfractionated heparin; LMWH, low molecular weight heparin; $T_{\text{max}}$, time to reach maximal plasma concentration or maximal anticoagulant activity; SC, subcutaneous; iv, intravenous.

**Figure 1** The half-life of the anticoagulant in this example is 17 h and $T_{\text{max}}$ is 1 h (as for fondaparinux). Catheter removal should thus be delayed at least 36 h and, because safety time should be at least 8 h, the next injection should at least 7 h after withdrawing the catheter (i.e. $8 \text{ h} - T_{\text{max}}$).
Figure 2 The half-life of the anticoagulant in this example is 4–5 h and $T_{\text{max}}$ is 4 h (as for LMWH). Catheter removal should thus be delayed at least 10 h and, because safety time should be at least 8 h, the next injection should be at least 4 h after withdrawing the catheter (i.e. $8 \text{ h} - T_{\text{max}}$).

The elimination half-life of LMWH increases by around 40% in patients with severe renal impairment (creatinine clearance = 30 ml min$^{-1}$) [29]. The dose of LMWH should thus be reduced, perhaps by a factor of two, in patients with severe renal disease. However, little if any adjustment seems necessary in patients with less impaired renal function. At this point, though, no specific recommendation has been validated in patients with mild renal impairment. A similar recommendation can be made for fondaparinux, and would apply to new antithrombotic drugs that depend on renal elimination.

**Restarting anticoagulation**

It takes about 8 h for an initial platelet plug to solidify into a stable clot that will remain intact after administration of additional anticoagulant medications [30]. This delay of 8 h is in accordance with Turpie’s meta-analysis on fondaparinux [14]. Indeed, there is a relationship between the risk of major bleeding and the first dose of anticoagulant: If the drug is started within the 6 h after surgery, it increases major bleeding without improving efficacy. The abnormally higher risk of major bleeding disappears 6 h after the end of surgery, i.e. 8 h after neuraxial puncture. It would thus seem prudent to delay restarting anticoagulant medications until a stable clot has been established. However, this does not imply waiting 8 h in each patient, because the onset time ($T_{\text{max}}$) of most anticoagulants is substantial. Instead, we recommend waiting for 8 h minus $T_{\text{max}}$. This strategy means that a total of 8 h will have elapsed before the peak of anticoagulation is re-established. In practice, the longer the $T_{\text{max}}$, the shorter the delay. For instance, if the $T_{\text{max}}$ is 4 h (as it is for LMWH), the safety delay would be 4 h; but if the $T_{\text{max}}$ is only 1 h (as it is for unfractionated heparin), the safety delay should be at least 7 h (Figs 1 and 2).

The obvious limitation of this approach is that $T_{\text{max}}$ defines the time of peak activity after anticoagulant administration. However, anticoagulation obviously begins at some earlier time and gradually increases until maximum effect is reached. Thus, waiting at least 8 h minus $T_{\text{max}}$ does not assure extremely low anticoagulant levels for a full 7 h. On the other hand, it seems a reasonable compromise between the risk of haemorrhagic complications and the risk of thrombosis.

**Other considerations**

There is considerable individual variability in baseline coagulation and in the response to anticoagulants. Obviously, the time to get complete haemostasis decreases with low platelet counts in patients with severe anaemia, and in those given dextran or antiplatelet agents.

Retroperitoneal haematoma resulting from posterior lumbar plexus blocks may cause femoral nerve compression and can even lead to life-threatening bleeding [31]. The risk factors for haemorrhagic complications associated with plexus blocks appear to be similar to those associated with spinal haematomas. Consequently, a similar approach to anticoagulation might be used in patients having deep plexus blocks, including posterior lumbar plexus and sciatic parasacral approaches.

**Management of regional anaesthesia in patients given selected, newer anticoagulants**

**Fondaparinux**

Recently, subcutaneous fondaparinux sodium, a synthetic pentasaccharide based on the active pentasaccharide sequence of heparin, was licensed for the prevention and treatment of venous thromboembolism. Fondaparinux is a synthetic indirect anti-Xa inhibitor and acts as an anticoagulant by binding antithrombin. Fondaparinux catalyses factor Xa inhibition by antithrombin, but has no effect on the rate of thrombin inactivation. Fondaparinux has a high bioavailability (nearly 100%) and a rapid onset of action (25 min) after subcutaneous administration. It reaches peak concentrations within 1–2 h. Terminal plasma half-life is 17 h in healthy patients, but is prolonged in patients with moderate renal impairment [32]. Fondaparinux received marketing approval for thromboprophylaxis after orthopaedic surgery in Europe and the USA in 2002. It is usually given once daily, at a subcutaneous dose of 2.5 mg, starting 6–12 h after surgical closure.

The manufacturer suggests that fondaparinux be started between 6 and 8 h after the end of surgery. An indwelling...
patients were treated with 2.5 mg.day\(^{-1}\) injections of fondaparinux, which is achieved by skipping one injection. This strategy was used successfully in a recent multicentre study (EXPERT) [33] in which 5704 patients were treated with 2.5 mg.day\(^{-1}\) of subcutaneous fondaparinux for 4 weeks after major orthopaedic surgery. A neuraxial or deep peripheral indwelling catheter was inserted in 1630 patients (29%). Overall, the rate of symptomatic venous thromboembolism was 1.0% and was similar in the patients with and without a catheter.

**Dabigatran etexilate**

Dabigatran etexilate is a new oral pro-drug of the direct thrombin inhibitor dabigatran, which is being developed by Boehringer Ingelheim [34, 35]. It is a low-molecular-weight, reversible thrombin inhibitor that binds to thrombin with a high affinity and specificity. Phase III trials with dabigatran etexilate are completed and it seems likely to be clinically available soon.

The half-life of dabigatran etexilate ranges from 14 to 17 h after multiple dose administration. After oral administration, plasma concentration increases rapidly, reaching a maximum after 2–4 h. In trials so far published, dabigatran etexilate was tested only postoperatively and was given orally once daily at 150 or 200 mg, starting with a half dose 1–4 h after the end of surgery. In a recent study of patients having total knee replacement, dabigatran etexilate did not differ significantly from subcutaneous LMWH in a non-inferiority trial [35]; it thus seems likely that the drug will soon be approved for routine clinical use because oral dosing is more convenient.

As the pharmacokinetic properties of this drug are established, we can speculate about its management with regional anaesthesia, which should be similar to that suggested for fondaparinux. Indeed, with dabigatran an indwelling epidural catheter should not be removed before 36 h (at least two half-lives) after the previous dose, and the next dose should not be given any sooner than 12 h after catheter removal. There thus needs to be a window of 48 h between two doses. In practice, this can be achieved by skipping one dose.

**Rivaroxaban**

Rivaroxaban (BAY 59–7939) is a potent, selective, oral factor Xa inhibitor, developed by Bayer Health Care. It belongs to a new class of oxazolidinone-based, active-site directed, factor Xa inhibitors. Factor Xa is located at the common intersection of the extrinsic and the intrinsic pathways for thrombin formation. Selective inhibition of factor Xa by rivaroxaban is expected to terminate the amplified burst of thrombin generation created during the hypercoagulable state that occurs after total knee replacement. This may result in better efficacy in preventing thrombus formation and therefore produce a better safety profile than other anticoagulants.

Phase III trials with rivaroxaban are completed and it seems likely that the drug will soon be approved for routine clinical use. As a prophylactic treatment, rivaroxaban should be administered once daily at a dose of 10 mg, starting 6–8 h after the end of surgery. The half-life ranges from 7 to 9 h after multiple dose administration, but can be higher in elderly patients. After an oral administration, a rapid increase in rivaroxaban plasma concentration is observed, reaching a maximum at about 2–4 h [36]. In all the orthopaedic trials, rivaroxaban was tested only postoperatively.

Because the pharmacokinetic properties of this drug are known [36], we can speculate about its management in conjunction with regional anaesthesia, which should be similar to that proposed for LMWH in Europe. Indeed with rivaroxaban, an indwelling epidural catheter should be removed at least 20 h (at least two half-lives) after the previous dose, and the next dose should be given 6 h after catheter removal.

**New oral anticoagulant agents in early development in major orthopaedic surgery**

Agents in the early stages of development (i.e. ongoing phase II studies) include several Xa inhibitors (Lilly 517717, YM150, DU-176b, apixaban [BMS-562247]). Glaxo-Smith-Kline, Sanofi-Aventis, and Hoffman La Roche also have phase II studies planned. There is also an orally active glycosaminoglycan enhancer (odiparcil [SB-424323]), which indirectly enhances thrombin inhibition via heparin cofactor II and has completed Phase II development. However, recommendations for use of these very new agents in conjunction with regional anaesthesia will need to wait until their pharmacokinetics will be better defined.

**Conclusion**

In summary, risk factors for haematoma related to regional anaesthesia/analgesia vary according to patient characteristics (age, weight, creatinine clearance and concomitant medications), the difficulties associated with the needle puncture, and the pharmacokinetic properties of the anticoagulant. Our recommendations are based on the pharmacokinetics of specific anticoagulants. Basically, we suggest allowing at least two half-lives to pass before catheter removal, and taking into account the time...
required to establish a stable clot and to reach maximum activity ($T_{\text{max}}$) before restarting anticoagulation.

In patients who receive chronic anticoagulant treatment, complete reversal of anticoagulation is probably not advisable due to the risk of postoperative thromboembolic complications. But when patients are not routinely anticoagulated, it appears preferable to avoid pre-operative anticoagulation before regional anaesthesia as this approach reduces the risk of anaesthesia-related haemorrhagic complications without increasing the risk of postoperative thrombotic complications. Patients should be observed for signs and symptoms of neurological impairment for 3 days after catheter removal. Clinical suspicion should prompt immediate diagnostic imaging, usually a magnetic resonance scan, and intervention as required.

The overall strategy we suggest the following.

Consider the risk/benefit ratio of neuraxial anaesthesia for each patient. In general, outcomes appear comparable with general and neuraxial anaesthesia [9–11]. Single-shot spinal anaesthesia is safer than insertion of an epidural catheter [21, 25].

Concomitant administration of medications affecting haemostasis such as antiplatelet agents, NSAIDs, or dextran represents an additional risk of peri-operative haemorrhagic complications, including spinal haematoma [21, 25].

Pre-operative initiation of anticoagulation is not required for efficacy. When begun within 2 h of surgery, anticoagulation may increase major bleeding [4, 5]. For example, fondaparinux is effective and not associated with an increased risk of major bleeding if started 8 ± 2 h after surgery; but it increases major bleeding without improving efficacy when the drug is started within 6 h after surgery [14].

For any anticoagulant, indwelling catheters should not be removed until at least two half-lives have passed [37]. The next re-injection depends on the time required to reach maximum concentration ($T_{\text{max}}$). The time necessary to optimise haemostasis is about 8 h; the minimum safety window can thus be estimated as 8 h – $T_{\text{max}}$.

Monitoring of anti-Xa concentrations in the plasma is no longer recommended, because concentrations do not predict the risk of bleeding [21, 25].

The presence of bleeding during needle puncture and catheter placement does not necessitate postponement of surgery. However, anticoagulant therapy should be delayed for 24 h after surgery when bleeding is observed [20, 21, 25].

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References


