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Review

Use of direct oral anticoagulants with regional anesthesia in orthopedic patients☆

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Abstract The use of direct oral anticoagulants including apixaban, rivaroxaban, and dabigatran, which are approved for several therapeutic indications, can simplify perioperative and postoperative management of anticoagulation. Utilization of regional neuraxial anesthesia in patients receiving anticoagulants carries a relatively small risk of hematoma, the serious complications of which must be acknowledged. Given the extensive use of regional anesthesia in surgery and the increasing number of patients receiving direct oral anticoagulants, it is crucial to understand the current clinical data on the risk of hemorrhagic complications in this setting, particularly for anesthesiologists. We discuss current data, guideline recommendations, and best practice advice on effective management of the direct oral anticoagulants and regional anesthesia, including in specific clinical situations, such as patients undergoing major orthopedic surgery at high risk of a thromboembolic event, or patients with renal impairment at an increased risk of bleeding.

1. Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), and its long-term complications cause significant morbidity, mortality and healthcare costs [1–3]. The risk of VTE is particularly high in patients who undergo major orthopedic surgery, such as total knee or hip replacement surgery [4]; therefore, these patients routinely receive anticoagulants for short-term perioperative and postoperative thromboprophylaxis [4,5]. Whether a patient is receiving long-term anticoagulation (for the treatment or prevention of VTE or for stroke prevention in patients with non-valvular atrial fibrillation [AF]) prior to orthopedic surgery should also be considered because appropriate anticoagulant management based on the risk of thromboembolism and bleeding is crucial in these patients [5]. Additionally, the use of regional neuraxial anesthesia poses a risk of hematoma in patients receiving anticoagulants, because of the insertion and removal of the needle and catheter.

The direct oral anticoagulants (OACs) apixaban, rivaroxaban, and dabigatran are approved for the prevention of VTE after elective knee or hip replacement surgery in the European Union and/or United States, as well as for the prevention of

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stroke in patients with non-valvular AF, and the treatment of VTE and prevention of recurrent VTE [6–11]. In Europe, rivaroxaban is also indicated for co-administration with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events after acute coronary syndrome with elevated cardiac biomarkers [10]. Apixaban and rivaroxaban are direct inhibitors of Factor Xa, whereas dabigatran is a direct inhibitor of thrombin. All three agents have been found to exhibit predictable pharmacokinetics and pharmacodynamics, and have a fast onset of action—reaching maximum plasma concentration rapidly after oral administration (apixaban, 3-4 hours; rivaroxaban, 2-4 hours; dabigatran, 0.5-2.0 hours) [6,8,10,12–15]. The half-lives of apixaban, rivaroxaban, and dabigatran are ~12 hours, 5-13 hours, and 11-14 hours, respectively [6,8,10]. Furthermore, the pharmacokinetic and pharmacodynamic characteristics are not influenced to a clinically meaningful extent by body weight, age, or gender, which collectively indicate that these direct OACs can be given as fixed dosing regimens without the need for routine coagulation monitoring [16–20]. The routes of drug elimination differ between the 2 drug classes: apixaban and rivaroxaban have multiple pathways including renal excretion (~27% and 66% [33% as active drug and 33% after metabolic degradation], respectively), whereas elimination of dabigatran is predominantly via the renal system (85%) [6,8,10,21]. In patients receiving dabigatran for the prevention of VTE after knee or hip replacement surgery, a dose reduction is required in those with moderate renal impairment (creatinine clearance 30-50 mL min^{-1}), those aged 75 years or over, and those taking concomitant mild-to-moderate P-glycoprotein inhibitors [8]. Owing to their mode of action, all anticoagulants can increase the risk of bleeding events. However, apixaban, rivaroxaban, and dabigatran did not pose any significantly increased risk of major bleeding events compared with enoxaparin in phase III clinical trials in the prevention of VTE after knee or hip replacement surgery [22–30]. Despite the clinical evidence on the safety and efficacy profile of direct OACs demonstrated in clinical trials, physicians—particularly anesthesiologists—need to be aware of how to minimize the risks of bleeding complications when treating patients who are taking an anticoagulant and are due to undergo surgery with regional anesthesia.

Regional anesthesia techniques have become increasingly popular because they offer several benefits over general anesthesia and traditional systemic analgesia, including reduced risk of mortality and less postoperative pain, thus facilitating early postoperative mobilization of the limbs and consequently reducing the chances of postoperative VTE [31,32]. Regional anesthesia is used in millions of operations each year and, at a time when the use of the direct OACs is growing, bleeding-related complications could arise if appropriate guidance is not followed [33]. This review aims to provide anesthesiologists with an overview of current data on the risk of hemorrhagic complications with direct OACs when using regional anesthesia, particularly in patients at a high risk of VTE, such as those undergoing major orthopedic surgery. Moreover, current guideline recommendations will be discussed and best practice in specific clinical situations, such as in patients with renal impairment who are at an increased risk of bleeding, will be highlighted.

2. Regional anesthesia and complications

The most common complications of regional anesthesia include postdural puncture headache (occurs in 0.1%-36% of patients but rarely lasts longer than 7 days) [34], backache (affects up to 11% of patients in the 5 days after the procedure) [35], and peripheral nerve damage (eg, transient paresthesia is estimated in up to 8%-10% of patients in the immediate days after regional anesthesia) [36]. Serious complications, such as spinal or epidural hematoma and epidural abscess, are rare and therefore difficult to study in detail [37]. For peripheral nerve block, neurological complications are extremely rare, ranging between 0.02% and 0.04% [38,39].

2.1. Risk factors associated with regional anesthesia

In a systematic review of 141 studies (n = 9559), neuraxial anesthesia was shown to be associated with lower rates of mortality (2.1% vs 3.1%; odds ratio [OR] 0.7; 95% confidence interval [CI] 0.54-0.90; P = .006), occurrence of DVT (odds reduction of 44%; OR 0.56; 95% CI 0.43-0.72; P < .001) and PE (odds reduction of 55%; OR 0.45; 95% CI 0.29-0.69; P < .001), among other outcomes [31]. A more recent observational study showed that neuraxial anesthesia was associated with a significantly reduced need for blood transfusions compared with patients receiving general anesthesia (28.5% vs 44.7%; OR 0.52; 95% CI 0.45-0.61; P < .0001) after simultaneous bilateral total knee replacement surgery [40].

2.2. Risk factors for the development of spinal hematoma

The overall incidences of hematoma in patients receiving neuraxial anesthesia (epidural and spinal) have been estimated to be as low as 1 in 220 000 and 1 in 320 000, respectively, in the absence of traumatic puncture and without the use of heparin or ASA [41]. However, the incidence of spinal hematoma increases with the presence of any risk factors, listed in Table 1, and more so if heparin anticoagulation is accompanied by traumatic puncture (increasing incidence rates to 1 in 2000 and 1 in 2900 for epidural and spinal anesthesia, respectively). For ASA therapy the risk is 1 in 8500 and 1 in 12 000 for epidural and spinal anesthesia, respectively [41,42]. An incidence of between 1 in 1000 and 1 in 10 000 has been estimated for neuraxial hematoma after central neural blockade in patients undergoing orthopedic procedures and receiving preoperative thromboprophylaxis with enoxaparin [43]. A recent review assessing spinal/epidural anesthesia complications in Finland from 2000 to 2009 showed the risk of developing a serious complication (defined as a potentially fatal event or an event of over 1 year in duration, including epidural hematoma) after