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Neuraxial anaesthesia and anticoagulant and antiplatelet agents: the ESA guidelines

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Guideline activity within the European Society of Anaesthesiology (ESA)

A focus group of the ESA Council members recommended in 2007 that the ESA should further its aims of improving the practice of anaesthesia throughout Europe by becoming involved in the production of evidence-based guidelines. Therefore, in 2008 the ESA Guideline Committee was formed to oversee these activities. One of the first guideline produced by the ESA is the recommendation on the role of regional anaesthesia in patients receiving anticoagulant, antiplatelet agents or both. In a recent ESA Newsletter (Autumn 2009), Andrew Smith (UK), chairperson of the ESA Guideline Committee, defined three elements for each ESA guideline: collaboration, transparency and simplicity. Although many national anaesthesia societies have prepared and published their recommendations in this field, European collaboration will hopefully help towards the harmonisation of clinical management, which may also help to improve standards.

Transparency implies that guideline production needs evidence, but may also require expert opinion. European experience on the risk of neuraxial haematoma sets the scarce research evidence in this field into its clinical context and produces an authoritative recommendation. Transparency ensures that disagreement between experts is explicitly declared. Simplicity should help to implement the guideline into our daily clinical practice. The ESA guideline on neuraxial anaesthesia in patients receiving anticoagulant or antiplatelet agents will be easily accessible in print (in the European Journal of Anaesthesiology in 2010) and on the ESA website. This Refresher Course abstract summarizes the key issues for quick guidance on wards and in the operating theatre.

Scope and limitations of guidelines

Practice guidelines are systematically developed recommendations that assist the clinician in decision making, specifically in timing regional anaesthesia in the clinical setting of a pharmacologically increased risk of bleeding. Recommendations may be adopted, modified, or rejected according to the clinical requirements and constraints. The use of recommendations does not guarantee prevention of neuraxial haematoma and peri-operative thrombosis, but improves risk stratification and awareness. Although intended as a scientific guideline, it might also assist in legal disputes.

Guidelines are subjected to revision as new evidence or experience becomes available. Specifically, the use of ultrasound-guided peripheral regional anaesthesia may, in the future, shorten the recommended withdrawal intervals of anticoagulant and antiplatelet agents.

Which anticoagulant and antiplatelet agents are relevant?

Anaesthetists are confronted with patients who are being treated with highly effective anticoagulant medications or new inhibitors of platelet function. Introduction of new substances into the market is expanding the drug repertoire. The following substance classes of anti-haemostatic drugs need to be identified by using a standardized pre-operative questionnaire of the patient's bleeding history and medication history: vitamin K-antagonists, unfractionated heparin and low-molecular-weight heparins, fondaparinux, heparinoids, direct thrombin inhibitors, factor X inhibitors, ADP receptor-antagonists, glycoprotein IIb/IIIa-inhibitors, and cyclooxygenase I-inhibitors.

Practical considerations

Patient assessment should be performed well in advance of elective surgical procedures in order to have time for further logistic, diagnostic and therapeutic consequences such as individual timing of surgery and nerve blockade, performance of appropriate drug-monitoring, and optimization of coagulation and pro-coagulant therapy [1]. Patients have to be informed about their specific risks for bleeding or thrombosis and give their consent to potential consequences.

Neuraxial haematoma

The risk of spinal haematomas is extremely low, but it can have dramatic neurological consequences for patients. The risk in patients receiving enoxaparin for thrombosis prophylaxis (40 mg once daily) was reported to be 1:18 000 after epidural anaesthesia and 1:156 000 after spinal anaesthesia, with bleeding complications occurring much more rarely in obstetrics (1:200 000) than in female orthopaedic patients (1:3 600) [2]. Others have found higher rates of up to 1:2 700 to 1: 19 505 [3-6]. Risk factors include the lack of guidelines, female sex, difficult puncture conditions and regional anaesthesia technique. The risk of haemorrhage is lowest in spinal anaesthesia and highest in catheter epidural anaesthesia [7].

Practical considerations

In order to minimize bleeding complications of regional anaesthetic techniques, care should be taken to avoid a traumatic puncture. The final decision to perform regional anaesthesia in patients receiving drugs that affect haemostasis has to be taken after assessment of the individual risk and benefit. If it is judged that the administration of the anticoagulant must not be interrupted, an alternative anaesthetic technique should be used. Spinal haematoma can occur late after surgery [8]. After performance of the block, the patient should be monitored at least until the effect of the regional anaesthesia is clearly declining, that is when there is a reduction in the extent of sensory block by two segments or a return of motor function. Particular attention should be given to persistent sensory or motor deficits, radicular back pain, pressure sensitivity in the puncture area and bladder dysfunction. When there is a clinical suspicion of neuraxial haematoma, appropriate diagnostic (MRI) or treatment measures (decompressive laminectomy) must be started immediately.

Time intervals for drug withdrawal

It is generally perceived that adhering strictly to the appropriate time intervals between the administration of anti-haemostatic drugs and regional blockade or removal of catheters improves patient safety and reduces the risk of haematoma formation. The ESA recommendations on time intervals are mainly based on pharmacology of the anti-haemostatic agents concerned rather than on (scarce) prospective, randomized clinical studies (Table 1). Drug combinations or interactions and reduced (renal or hepatic) elimination alter pharmacokinetics significantly, increase the risk for bleeding and limit the value of recommended withdrawal times.

Aside from recommending time intervals, the ESA guideline also aggregates information on currently available anti-haemostatic agents including their pharmacology, indications and side effects.

It is important to remember that anti-haemostatic agents are prescribed because of a risk of thrombotic manifestations. Surveillance for postoperative thrombosis or ischaemia is essential during the postoperative recovery period, especially in patients receiving antiplatelet therapy. An early resumption of treatment postoperatively is essential.

Table 1

ESA recommendation for time intervals before and after neuraxial puncture or catheter removal

	Time before puncture/ catheter removal	Time before puncture/ catheter removal
Unfractionated heparins (for prophylaxis, $\leq 15\,000$ IU/day)	4-6 h	1 h
Unfractionated heparins (for treatment)	iv 4-6 h sc 8-12 h	1 h 1 h
Low-molecular-weight heparins (for prophylaxis)	12 h	2-4 h
Low-molecular-weight heparins (for treatment)	24 h	2-4 h
Fondaparinux (for prophylaxis < 2.5 mg/day)	36-42 h	6-12 h
Rivaroxaban (for prophylaxis < 10 mg/day)	22-26 h	2-4 h
Apixaban (prophylaxis, 2.5mg b.i.d)	10-15 h	2-4 h
Dabigatran (prophylaxis, 150-220 mg)	contraindicated according to the manufacturer	
Coumarins	INR < 1.4	after catheter removal
Hirudins (lepirudin, desirudin)	8-10 h	2-4 h
Argatroban ‡	4 h	2 h
Acetylsalicylic acid	none	none
Clopidogrel	7 days	after catheter removal
Ticlopidine	10 days	after catheter removal
Pasugrel	7 days	after catheter removal
Ticagrelor	48-72 h	after catheter removal
NSAIDs	none	none

INR, international normalized ratio; IU, international unit; NSAIDs, non-steroidal anti-inflammatory drugs.

* All time intervals refer to patients with normal renal function.

‡ Prolonged time interval in patients with hepatic insufficiency.

Important points about antithrombotic drugs

Unfractionated heparin

In the ASA closed claims analysis, spinal epidural haematoma occurred most frequently in vascular surgery patients, suggesting that this population is at an increased risk [9]. The risk of haemorrhage after epidural anaesthesia and subsequent intra-operative heparinization is not increased if heparinization is delayed for 1 h after spinal or epidural puncture. Removal of epidural catheters should be not be carried out until at least 4 h after the end of heparin administration with normalization of coagulation parameters (aPTT, ACT).

If a bloody puncture occurs in patients in whom intra-operative heparinization is planned, it is recommended that low-dose anticoagulation (for example, 5000 IU) should be avoided for 1–2 h and full heparinization should be avoided for 6–12 h, with the operation being delayed to the next day if necessary. Alternatively, to avoid delays, epidural catheter placement can be carried out the evening before surgery. This is particularly recommended in cardiac surgery using extracorporeal circulation [10]. In view of the limited benefits of neuraxial blockade in cardiac surgery, with no major effect on morbidity and mortality and considering the significant risks, it is disputable whether spinal and epidural techniques are justified at all or should be abandoned in this particular patient population [11].

Low-molecular-weight heparins (LMWH)

A meta-analysis of studies on the timing of thromboprophylaxis showed that LMWH given 12 h pre-operatively does not reduce the risk of thrombo-embolism compared with a postoperative regimen [12]. Since it is known that anti-thrombotic drugs increase the risk of spinal epidural haematomas after neuraxial blockade, a postoperative start may be advantageous.

To avoid bleeding complications, there should be a time interval of at least 12 h between subcutaneous administration of LMWH in prophylactic dosages and the placement or removal of an epidural catheter [6, 13]. At a therapeutic dosage, catheter placement or removal should be delayed for at least 24 h after the last administration. Whether a 24-h interval is acceptable in relation to the thrombo-embolism risk needs to be considered on an individual basis. In cases at high risk of thrombo-embolism (for example, mitral or double mechanical valve replacement) one should refrain from neuraxial blockade and continue the administration of LMWH.

Following spinal or epidural puncture, or after removal of a spinal or epidural catheter, repeat administration of LMWH should be delayed for at least 2–4 h.

Fondaparinux

The EXPERT study with a total of 5 387 patients [14] used a time interval of 36 h before catheter removal and 12 h after catheter removal before the next dose of fondaparinux for thrombosis prophylaxis. In cases of therapeutic anticoagulation with fondaparinux (5 - 10 mg per day) neuraxial anaesthesia should not be performed due to the substantial risk of accumulation.

Rivaroxaban

A time interval of 22-26 h between the last dose of rivaroxaban (10 mg) and puncture or catheter withdrawal is recommended. After catheter withdrawal the next dose of rivaroxaban may be given after 2-4 h.

Dabigatran

A time interval of 34 h between the last dose of dabigatran and puncture or catheter withdrawal can be extrapolated from pharmacokinetic data. However, the manufacturer advises against the use of dabigatran in the presence of neuraxial blockade. This warning has medico-legal consequences if a spinal epidural haematoma occurs.

Vitamin K antagonists (phenprocoumon, warfarin)

Therapeutic anticoagulation with vitamin K antagonists represents an absolute contra-indication to neuraxial blockade. Vitamin K antagonists should only be administered after the catheter has been removed.

Direct thrombin inhibitor: argatroban

Patients with acute heparin-induced thrombocytopenia frequently suffer from multiple organ failure including coagulation disturbances, making neuraxial blockade not advisable.

Danaparoid, desirudin, lepirudin

It is preferable to carry out single-shot spinal anaesthesia without pre-operative danaparoid administration and avoid the use of catheters. In general, it is advisable to maintain as long an interval as possible (at least 8–10 h) between the administration of desirudin and lepirudin and neuraxial puncture and to avoid combinations with other anti-thrombotic agents.

Important points about platelet inhibitors

Acetylsalicylic acid and thienopyridines

On the basis of the available data, it can be assumed that non-steroidal anti-inflammatory drugs – including acetylsalicylic acid, by themselves do not lead to an increased risk of spinal epidural haematomas [15-17] and thus do not represent a contra-indication. A higher rate of complications has been observed in both surgical and medical patients when heparins were administered simultaneously [18].

Neuraxial regional anaesthesia should only be carried out if a time interval of 7 days between the last intake of clopidogrel and the neuraxial blockade is possible (10 days after the last administration of ticlopidine).

Dual antiplatelet therapy and the risk of cardiovascular events

It is recommended that patients with acute coronary syndromes or stent implantation should continue to take acetylsalicylic acid on a lifelong basis [19]. With bare metal stents (BMS), dual platelet aggregation inhibition should be administered for at least 4-6 weeks after implantation, and with drug-eluting stents (DES) these should be taken for 12 months [19]. Elective surgery should be postponed until the mandated clopidogrel therapy ends and the surgery can be performed with acetylsalicylic acid only. In an emergency, all peri-operative care providers should be aware of the increased risk of intra- and postoperative bleeding. In semi-elective or urgent cases the management should be tailored to the thrombosis/bleeding tolerance. Dual antiplatelet therapy should be re-started postoperatively as soon as possible. In patients with acute coronary syndromes and emergency stent implantation, discontinuation of clopidogrel for the sake of catheter withdrawal may be life-threatening.

Glycoprotein IIb/IIIa inhibitors

Cardiac surgery procedures are usually conducted as emergencies with continuing combined anticoagulation. In these situations, central nervous blockade is contra-indicated. If a catheter has to be removed after the administration of glycoprotein IIb/IIIa antagonists, waiting at least 48 h after abciximab, or 8–10 h after tirofiban or eptifibatide is recommended.

Important points about thrombolysis and alternative medicine

As thrombolysis usually represents an emergency indication that cannot be postponed – for example, after severe pulmonary embolism or myocardial infarction, time intervals cannot be adhered to when the epidural catheter is already in place. It appears to be safer to leave the catheter in-situ even during thrombolysis.

Warnings against neuraxial puncture in the presence of alternative medicines and recommendations to withdraw these substances pre-operatively are at present unjustified, particularly for preparations manufactured in Germany (where contents are usually clearly listed).

Peripheral nerve blocks

Peripheral nerve blocks cause less serious complications and are devoid of the risk of spinal epidural haematoma. Peripheral nerve blocks have been divided into two groups according to their bleeding risk [20]. Performance of superficial peripheral nerve blocks such as axillary plexus block, femoral nerve block or distal sciatic nerve block are not contra-indicated in the presence of anti-haemostatic agents if there is a normal bleeding history. However, for deep peripheral nerve blocks (close to vessels that cannot be compressed such as infraclavicular nerve block and lumbar sympathetic blockade) time intervals established for neuraxial blockade should be followed.

Key learning points

- Pre-operative patient evaluation includes the assessment of bleeding history and medication history
- In patients taking anti-thrombotic and/or antiplatelet agents an individualized risk stratification targeted towards minimizing risks for bleeding and thrombosis is recommended
- With a high risk of bleeding avoidance of anti-haemostatic drug combinations and withdrawal of anti-haemostatic agents should be considered
- Careful timing of regional anaesthesia includes time intervals before and after puncture or catheter removal in accordance with the ESA recommendations
- Intra-operative and postoperative awareness of all disciplines involved in the management of patients taking anti-haemostatic agents is necessary for the immediate diagnosis and treatment of bleeding complications and thrombotic manifestations

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