

Regional anaesthesia under anticoagulants

Recommendations of the working group on Perioperative Coagulation of the ÖGARI

Valid until: end of 2010

1. National and European recommendations

The recommendations for therapy interruption periods prior to central and peripheral blocks were developed in 2005 by the working group on perioperative coagulation of the Austrian Society of Anaesthesia, Resuscitation and Intensive Care (ÖGARI) (1). The market launch of new commercial anticoagulants and the growing body of knowledge related to the special problems associated with dual antiplatelet therapy following coronary stent implantation make it necessary to update our national recommendations. This article is intended to present the most current national recommendations, which also take into consideration the current international recommendations of the European Society of Anaesthesiology concerning neuraxial anaesthesia and anticoagulants. *Current changes highlighted in cursive.*

2. Background

2.1 Risk of spinal haematomas

Case reports document the occurrence of puncture-related haematomas in patients receiving anticoagulants, whereby individual reports show that the effects of bleeding with local/regional anaesthetics can be disastrous for patients, especially in cases of spinal haematomas. The incidence of spinal haematomas is very low in patients with normal coagulation. A European retrospective analysis found an incidence of 1:18,000 following epidural puncture, 1:156,000 following spinal puncture. The bleeding risk is lower in the field of gynaecology and obstetrics (1:200,000) than among orthopaedic patients (1:3.600) (2). Risk factors for a spinal haematoma include bloody aspiration, traumatic puncture, anatomical changes (e.g. Spina bifida, Ankylosing spondylitis) and anticoagulant therapy (3). Due to the rarity of spinal haematomas, there are no prospective, interventional studies for statistical reasons. The bleeding risk can be reduced if the risk-related procedure (puncture, catheter removal) is performed when the antithrombotic medication has reached a pharmacokinetic trough concentration.

In the case of neuraxial blocks the bleeding risk is lowest for single-shot spinal anaesthesia, followed single-shot epidural anaesthesia, with catheter procedures posing the highest risk. Placement of an epidural catheter appears to be just as critical to the formation of a haematoma as the removal of the catheter because the tissue is traumatized during both procedures. As a result, the recommended time intervals in Table 1 should be observed prior to removing the catheter. Careful fixation of the catheter with adhesive tape is required here, along with subcutaneous tunneling, as needed.

2.2 Categorisation of bleeding risk with peripheral blocks

In 2005 the AGPG categorised blocks into those associated with bleeding risk and those not associated bleeding risk (1). The 2007 revision recategorized sciatic nerve blocks into the category of blocks not associated with bleeding risk: In cases with an unfavourable risk-benefit analysis for the application of a general anaesthetic, the combination of a sciatic nerve block with a femoral nerve block appears to be safer and less susceptible to bleeding risk than a neuroaxial block.

Ultrasound-guided blocking techniques have since been introduced in many Austrian hospitals. The current revision should now consider the safety gains associated with this technique, whereby the ultrasound-guided blocks are to be classified in the category of blocks not associated with bleeding risk.

Prior to peripheral blocks with bleeding risk and prior to peripheral blocks without bleeding risk in patients with abnormal bleeding histories we continue to urge compliance with therapy interruption times similar to those recommended prior to neuraxial puncture. Compliance with the recommended therapy interruption times is not mandatory prior to peripheral blocks without bleeding risk in patients with normal bleeding histories. However, due to the possibility of secondary injury to the soft tissue as the result of compression caused by the haematoma or infection of the haematoma, in these cases it is required to a) perform a strict and critical risk-benefit analysis on the individual patient prior to applying the block, b) exhaust all other non-invasive treatment alternatives, c) use an atraumatic blocking technique, and d) provide continuous, postoperative follow-up monitoring by a physician who is able to identify and treat any possible complications. The last of these requirements assumes a functional cooperative relationship across departments within the medical facility.

3. General principles

3.1 Patient orientation concerning bleeding risk and postoperative follow-up

Patient information concerning the risk of bleeding associated with local/regional anaesthesia is always required and must be documented.

Following the application of local/regional anaesthesia, an anticoagulated patient must remain under continuous observation at least until the effect of the anaesthesia has decreased considerably. In order to enable the early detection of the initial signs of paresis under continuous application of local anaesthesia, the lowest possible effective local anaesthesia concentration should be used. During follow-up special attention should be paid to persistent sensory or motor impairments, radicular back pain, and bladder dysfunction. Should any of these occur, the anaesthetist is to be notified right away.

3.2 Coagulation diagnostics prior to regional anaesthesia

A bleeding history must be carefully compiled at the start of any evaluation for a regional anaesthesia indication (10). Further coagulation diagnostics must be performed (including a clarification of primary haemostatic capacity) in the case of an abnormal bleeding history. It should be noted that the most common inherited coagulopathy, the von Willebrand Syndrome, does not become clinically symptomatic until after anticoagulants have been administered. It is not possible to predict an increased bleeding tendency using conventional coagulation testing alone (aPTT, PTT, fibrinogen levels, platelet counts).

The interindividual variability of the pharmacokinetics and pharmacodynamics of anticoagulants is unknown without adequate drug monitoring. The therapy interruption period shown in Table 1 is insufficient in cases where elimination of a medication is impaired. In such a situation, consideration should be given to drug monitoring or switching to an anticoagulant that is eliminated some other way. The options for the emergency reversal of anticoagulant effects are summarised elsewhere (12).

3.3 Management of manifest bleeding complications

All specialisations and professional groups charged with the management of patients receiving local/regional anaesthesia are required to undergo adequate training and continuing education courses. In cases of suspected haematomas following local/regional anaesthesia, diagnostic and therapeutic measures must be initiated immediately. Magnetic resonance imaging is the method of choice for the diagnosis and localisation of neuraxial bleeding; alternative methods include myelography or computer tomography. A neurosurgical procedure to alleviate bleeding must be performed within 8 hours in order to ensure a favourable prognosis for patients with neuraxial bleeding. In the case of catheters (e.g. patient-controlled analgesia) the anaesthesiologist should check up on the patient at appropriate intervals (at least once daily) and all staff involved in the management of the patient must pay close attention in order to improve the prognosis of patients with neuraxial bleeding.

3.4 Alternatives to local/regional anaesthesia

General anaesthesia should be considered as an alternative to perioperative local/regional anaesthesia based on an individual risk-benefit analysis.

4. Key messages about individual anticoagulants

Reviews on the pharmacology, side effects, and contraindications for the substances are provided elsewhere (1,5,6).

This recommendation concerning therapy interruption periods prior to a procedure (puncture and/or catheter removal) is strictly based on compliance with twice the half-life period of the respective substance for patients. Currently < 25% of the pharmacodynamic effect is to be anticipated (7). As a result, the therapy interruption periods presented in Table 1 are shorter than the times that our working group and other international experts have previously recommended. However, due to the fact that half-life periods vary among individuals and can sometimes be unpredictable, especially in patients with organ dysfunctions and a reduced elimination capacity (e.g. renal insufficiency), suitable drug monitoring can provide additional assistance in scheduling the procedure (Table. 1).

The current literature contains reports of therapy interruption times observed prior to the next dose of anticoagulant, which have been set mostly at random. No research has been performed to determine the point in time at which a sealed vascular lesion at the puncture site stops bleeding due to the presence of anticoagulants. This would be of special interest for direct thrombin inhibitors because they can also cause thrombus regression. The dose and efficacy of the anticoagulants to be applied are likely to have an influence on blood clot stability. Slow-acting substances can be administered earlier than fast-acting substances. Certain fast-acting substances, such as prostaglandins, are

typically administered at low doses from a haemostaseological standpoint. As a result, an immediate start following a procedure seems less advisable. Table 1 includes the pharmacokinetic ratios up to the maximum effect. However, since the onset of effect also varies among individuals and can sometimes be unpredictable, the value of the recommendation grade should be considered low for a therapy interruption period following a procedure. This time period will be longer in the case of traumatic, bloody punctures. The value of the recommendation grade for clinical, neurological follow-up here is also high in order to enable the early diagnosis of any bleeding.

Unfractionated heparin: The therapy interruption times are to be complied with in the case of prophylactic doses for elective procedures (Table 1). In traumatology, unfractionated heparin is often administered initially as thrombosis prophylaxis (5000 IU upon admission) and combined with the postoperative administration of low molecular weight heparin. When there is an urgent indication for regional anaesthesia (e.g. risk of aspiration), then peripheral blocks or a single-shot spinal anaesthesia are justifiable in such an acute situation, even before the 3-hour therapy interruption period has lapsed. As always, careful neurological follow-up must be provided here. *The next prophylactic heparin dose can be administered 1 h following puncture/catheter removal (1-2 h following bloody puncture).*

In the case of therapeutic doses, it is recommended to run lab tests to ensure normalisation of aPTT or ACT prior to a procedure. Full heparinisation, for example in heart surgery, should not be performed until 6-12 h have lapsed (e.g. catheter placement on the day before the operation).

According to a clinical observation from the field of vascular surgery, intraoperative heparinisation is safe approx. 2 h following puncture or catheter placement. But since there are so few study data, the working group is unable to formulate a recommendation on this. In cases of a normal, standardised bleeding history and heparin monotherapy this procedure could be safe; however careful, neurological follow-up monitoring must be provided. Alternative recommendation: catheter placement on the day before the operation.

Low molecular weight heparins: Compliance with the therapy interruption times is required in the case of prophylactic doses (Table 1). Due to the long interruption time of 24 h for therapeutic doses (Table 1), an indication for regional anaesthesia is only recommended following a careful risk-benefit analysis for the individual. Bridging therapy with unfractionated heparin is possible.

Pentasaccharide: Typically, thrombosis prophylaxis is not administered until 6 h after the operation. As a result, bleeding risk does not result from the placement of the regional anaesthesia but rather when the catheter is removed. Long half-life periods require long therapy interruption periods (Table 1); but these are not associated with diminished efficacy for thrombosis prophylaxis (4). *The antithrombin-induced selective inhibition of factor Xa cannot be quantified by either aPTT, PTT/INR or bleeding time.*

Direct thrombin inhibitors: A discontinuation of therapy is generally contraindicated for the indication of these substances to treat heparin-induced thrombocytopenia (HIT) II with or without manifest thromboses due to the high risk of thrombosis. Regional anaesthesia is thus rarely indicated for patients with HIT. The following should be observed when administering thrombosis prophylaxis substances (e.g. for patients with HIT in their case history): Bleeding is often observed with hirudins. In addition to therapy interruption times, lab tests are recommended to ensure normalisation of aPTT (*with the use of Actin FS or Neothromtin*) or ECT. Cave: Renal insufficiency. Short therapy interruption times are recommended based on the short half-life periods for argatroban and bivalirudin. Cave: Liver failure with argatroban and renal failure with bivalirudin.

Dabigatran (Pradaxa®) is a direct thrombin inhibitor administered orally as thrombosis prophylaxis following hip and knee replacement surgery. *Ecarin clotting time can be used to measure the pharmacodynamic effect of dabigatran. A prolonged aPTT is not dose-related. PTT is barely influenced.*

Rivaroxaban (Xarelto®) is a direct factor Xa inhibitor administered orally as thrombosis prophylaxis following hip and knee replacement surgery in adults. *With respect to therapy interruption times, the manufacturer recommends an interval of at least 18 h (e.g. prior to epidural catheter removal) and an interval of 6 h prior to the next administration, although no study data are available to support this.*

The prothrombin time with neoplastin as the reagent can be used to measure the pharmacodynamic effect of rivaroxaban (PTT in s, not as INR). Although rivaroxaban also prolongs aPTT and HepTest, depending on the dose, these tests are not recommended for monitoring by the manufacturer. There is no calibration standard currently available for measuring anti-Xa activity.

Table 1. Recommended anticoagulant therapy interruption times for local/regional anaesthesia (in patients with normal elimination capacity and functioning organs) – Update 2009.

Substances	End of therapy + Lab test result prior to puncture / catheter removal	Start of therapy following puncture / catheter removal at the earliest
MEDICATIONS THAT TARGET PLASMATIC COAGULATION:		
Unfractionated heparins		
s.c. or continuous i.v. (aPTT < 1.5 norm) therapeutic dose	3 h aPTT or ACT within the reference range (> 3 h)	1 h 6-12 h (i.v.)
Low molecular weight heparins		
prophylactic dose	11 h	2 h
therapeutic dose	24 h + anti-Xa activity within the reference range	2 h
Direct thrombin inhibitors		
Desirudin, Lepirudin	4.5 h + aPTT within the reference range	4 h
Argatroban	2 h + aPTT within the reference range	4 h
Bivalirudin	1 h + aPTT within the reference range	4 h
Dabigatran	26 h	4 h
Synthetic pentasaccharide		
Fondaparinux (≤ 2.5 mg/day)	36 h	6 h
Direct factor Xa inhibitors		
Rivaroxaban	16 h	3 h
Heparinoids (s.c.)	anti-Xa activity within the reference range (approx. 2 days)	2 h
Vitamin K antagonists	INR < 1.4 (approx. 2 days)	immediately
Recombinant activated protein C	2 h	4 h
MEDICATIONS THAT TARGET CELLULAR COAGULATION:		
Adenosine diphosphate (ADP) receptor antagonists		
Clopidogrel	7 days ^a	immediately
Ticlopidin	10 days ^a	immediately
Cyclooxygenase inhibitors		
Acetylsalicylic acid - monotherapy	not required	immediately
Non-steroidal anti-rheumatics	not required	immediately
Selective cyclooxygenase-II inhibitors	not required	immediately
Glycoprotein IIb/IIIa inhibitors		
Abciximab	48 h	6 h
Tirofiban	8 h	6 h
Eptifibatide	4 h	6 h
Antiaggregatory prostaglandins		
Iloprost	1 h	6 h
Prostacyclin (Epoprostenol)	10 min	immediately
Prostaglandin E ₁	10 min	immediately

aPTT = activated partial thromboplastin time, INR = international normalized ratio

a: according to the manufacturer's specifications; always following platelet regeneration > 72 h

Heparinoids: Due to the alternative anticoagulation with heparin-induced thrombocytopenia type II and difficulties in securing suppliers, it can be assumed that Danaparoid will only be used rarely in day-to-day clinical situations. If regional anaesthesia is planned, then preoperative thrombosis prophylaxis with the heparinoid (Danaparoid) should not be administered. Due to the long half-life period a catheter procedure should not be employed. Cave: Renal failure.

Oral anticoagulants (coumarins): Due to the long half-life period and its variability among individuals, a neuraxial regional anaesthesia without a therapy interruption period is contraindicated. Bridging therapy with low molecular weight heparins is recommended in the case of any interruption. Reversal with coagulation factor concentrate (PPSB) or fresh frozen plasma is generally not indicated for the sole purpose of administering regional anaesthesia. Catheters should be removed postoperatively prior to oral administration of a therapeutically effective anticoagulant.

Recombinant activated protein C: Regional anaesthesia will rarely be indicated for critically ill patients with sepsis and multiple organ failure. However, an increased bleeding risk is to be anticipated with recombinant activated protein C and antithrombin medications at higher doses.

Acetylsalicylic acid (Aspirin): While aspirin does increase spontaneous and perioperative bleeding risk 1.4-2-fold, the extent of the bleeding rarely requires a transfusion. However, a therapy interruption period is recommended prior to intracranial operations, due to the bleeding risk associated with the procedure (8). The safety of aspirin (as a monotherapy) is based 1.) on three studies with approx. 1,050 patients with neuraxial anaesthesia while taking aspirin and 2.) especially on clinical experience, whereby no spinal haematomas have ever been observed despite the common use of aspirin. The

bleeding risk may be lower in pregnant patients taking aspirin than in non-pregnant patients, due to physiological prothrombotic coagulation status (4).

Thus, based on the recommendations of the ESA (as opposed to the Austrian recommendations from 2005) compliance with therapy interruption times for patients taking aspirin prior to regional anaesthesia is no longer urgently recommended. This recommendation is valid for aspirin regimens that are not combined with other anticoagulants and for patients with a normal bleeding history (10). In the case of abnormal bleeding histories or combination therapies, a 48-hour interruption in aspirin intake is advisable prior to single-shot spinal anaesthesia with atraumatic needle while a 72-hour interruption is advisable prior to all other neuroaxial procedures. *However, in the case of those patients who are supposed to continue receiving aspirin perioperatively as secondary prophylaxis (e.g. following coronary stent implant surgery) it appears to be more feasible and safer to interrupt thrombosis prophylaxis only prior to the scheduled puncture while on aspirin. This can be achieved by foregoing the administration of the low molecular weight heparin on the evening prior to the operation (or 11 h prior to puncture) or by not starting prophylaxis administration until after the operation (or after the block). Likewise, the time window should be 11 h between the administration of the low molecular weight heparin and the removal of a peridural catheter while on aspirin in order to avoid combining both substance groups at the time of the operation.*

An emergency situation can become problematic if the patient took aspirin and then received unfractionated heparin immediately upon admission to hospital. An individual risk-benefit analysis is recommended here, which takes into account the increased bleeding risk due to the combination of both substance groups at the time of the procedure. Whether it is justifiable to begin heparinisation 1 h following single-shot spinal anaesthesia (and not immediately upon admission) based on the risk of thromboembolism must be assessed on a case-by-case basis. In cases of an increased risk of thromboembolism heparin should be administered without any block.

Dual antiplatelet therapy:

For patients on dual antiplatelet therapy (usually clopidogrel and aspirin) the treatment goal is not the monodisciplinary maximisation of safety with respect to bleeding complications, but rather the interdisciplinary optimisation of safety with respect to (stent) thrombosis and bleeding risk. The risk of stent thrombosis and myocardial infarction in patients with coronary stents depends on the individual thrombosis risk and the features of the stent (location, length, coating, time of implantation) (11). The American Heart Association recommends that aspirin be taken for life, clopidogrel for 1 month (uncoated stent) or 3-12 months (sirolimus- or paclitaxel-coated stent). No elective operation and regional anaesthesia should be performed during a therapy interruption period prior to the scheduled time for the completion of clopidogrel administration. It should generally be noted that an individual, interdisciplinary risk-benefit analysis is always required for these patients prior to starting a therapy interruption period.

No neuraxial and bleeding-risk-associated peripheral regional anaesthesia should be administered while the effect of clopidogrel is ongoing because clopidogrel can cause spontaneous and perioperative bleeding requiring transfusions. If clopidogrel is interrupted, regional anaesthesia can be performed under monotherapy with aspirin. A bridging therapy with platelet inhibitors having a short-term effect (e.g. tirofiban) is currently being studied. The reversal of the clopidogrel effect with desmopressin, antifibrinolytics, platelet concentrates, for example, is generally contraindicated for the sole purpose of administering regional anaesthesia. Monitoring of the platelet function inhibition (e.g. with aggregometry) is advisable for diagnostic purposes. It should be ensured that thrombosis prophylaxis (low molecular weight heparins) is not initiated until after the puncture and that appropriate therapy interruption times are observed prior to catheter removal. A rapid post-operative restart of the clopidogrel therapy is recommended to reduce perioperative stent thrombosis risk. Catheters should be removed prior to restarting clopidogrel therapy (especially in cases of a high initial loading dose).

Non-steroidal anti-rheumatics (NSAR): Similar to the case with aspirin, compliance with therapy interruption periods prior to neuraxial or blood-risk-associated peripheral regional anaesthesia is no longer urgently recommended for patients with normal bleeding histories receiving monotherapies. If it is necessary to rule out an anticoagulant effect for an NSAR with certainty, then a waiting period of 2 half-life periods is recommended. *Due to the fact that patients are usually receiving a combination therapy with thrombosis prophylaxis when the time comes to remove a peridural catheter, a time window of 2 half-life periods for the NSAR is recommended prior to removing the peridural catheter. The same is valid for the placement of a peridural catheter for preoperatively initiated thrombosis prophylaxis. Pain should be treated during this phase with analgesics that do not affect platelet function inhibition.*

Glycoprotein IIb/IIIa inhibitors: Neuraxial regional anaesthesia is generally contraindicated due to the fact that these substances are used in combination with aspirin and anticoagulants in cases of acute coronary syndrome and the ensuing cardiac surgery procedures are emergency operations. Short therapy interruption periods are recommended for the possible new indication of tirofiban for bridging therapy during clopidogrel interruptions based on the short half-life period (1.5 h) (Table 1).

Fibrinolysis: Due to the incidence of spontaneous spinal haematomas and a clinically relevant increase in bleeding risk, neuraxial regional anaesthesia is contraindicated. If an emergency fibrinolysis is necessary after a peridural catheter has already been placed, then it is recommended that this catheter not be removed until the therapeutic effects have abated. Fibrinogen levels can be determined and thromboelastometry performed for monitoring purposes.

Herbal medicines: Although there are few case reports of spinal haematomas due to excessive garlic consumption, the bleeding risk is considered low. Similar to the case with aspirin, compliance with therapy interruption periods is not recommended for herbal medicines prior to neuraxial regional anaesthesia in patients with normal bleeding histories.

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