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Review

PERIPHERAL NERVE BLOCKS IN PATIENTS ON ANTITHROMBOTIC DRUGS – A RESCUE OR AN UNNECESSARY RISK?

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ABSTRACT – Bleeding complications after peripheral nerve blocks (PNBs) in patients treated with an antiplatelet agent and/or an anticoagulant drug are rare, with estimated incidence of 0.67% (0.51–0.83%). However, they can result in significant patient morbidity and may require follow-up investigations and interventions. The evidence for bleeding risks and complications after PNB is very low or nonexistent, therefore, recommendations and guidelines are based on retrospective analyses, case reports, expert opinions and expert panel consensus. In the manuscript, an expert panel consensus on classification of PNBs according to the potential risk of serious bleeding complications is presented. The risks of bleeding depend on the location (vicinity of the vessels and critical structures at risk from the mass effect of a hematoma), block depth (which influences needle visibility), associated comorbidities and anticoagulation status, body habitus, site compressibility, whether the bleeding or hematoma are easy or not to assess and how easy or not an intervention may be applied to prevent or treat bleeding. Also, technical factors are considered: type and size of the used needle, technical difficulties, multiple attempts, needle passes and bloody tap, use of catheters and type of nerve location technique (USG versus *blind* techniques) and operator experience.

In all patients on antithrombotic drugs, benefits vs. risks should be weighted. A bleeding risk should be minimized with the optimization of patient's coagulation: appropriate antithrombotic drug timing before PNB, dose of antithrombotic drug, indication for the drug and risk factors that may influence drug pharmacokinetics (bodyweight, age, renal and hepatic function). Superficial PNBs may be performed in the presence of antithrombotic drug. For deep PNBs, a recommendations for neuraxial procedures should be considered.

Keywords: *peripheral nerve block, anticoagulants, platelet inhibitors, bleeding complications, regional anesthesia*

Introduction

Single-shot and continuous peripheral nerve blocks (PNBs) are widely used in clinical practice. Evidence shows that in certain circumstances these techniques may be preferable over general anesthesia because of an excellent postoperative analgesia and a lower incidence of postoperative complications such as nausea and vomiting.[1]

Bleeding complications after PNBs are very rare but can result in significant patient morbidity and may require follow-up investigations and interventions. The evidence for bleeding risks and complications after PNB is very low or nonexistent (because of their rarity), the same means for reports of positive outcome. One of the reasons for the rare occurrence of bleeding complications may be the enhanced safety from the implementation of guidelines in the management of patients with altered coagulation undergoing regional anesthesia. Consequently, recommendations are based

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on retrospective analyses, case reports, expert opinions and expert panel consensus.[2] Nevertheless, the absence of evidence for complications should not be interpreted as evidence of absence of complications. Since bleeding complications in neuraxial anesthetic techniques are likely to be devastating, anesthesiologists are sensitized to performance of regional anesthesia techniques in patients using antithrombotic drugs. In selected patients, peripheral nerve blocks are considered a solution when there is a contraindication for neuraxial technique (paravertebral vs. epidural). But, is a risk of PNB in a patient on antithrombotic drug in acceptable range?

Bleeding risk in peripheral nerve blocks

The estimated incidence of bleeding complications associated with PNBs in patients treated with an antiplatelet agent and/or an anticoagulant was low (0.67% (0.51–0.83%)).[3] As majority of cases in literature necessitated further observation for hemodynamic instability or organ damage, additional investigations or interventions and most probably only more severe and clinically obvious complications were included, with incidence of all bleeding complications being under-represented. Wound hematoma is a rare complication of PNBs, but carries risks: the need for potential surgical evacuation, transfusion and nerve damage by compression. In an analysis of *deep blocks*, several severe bleeding complications have been identified (retroperitoneal hematoma, hemothorax, spinal hematoma…). There was no case of transient or long-term neuropathy identified or related to bleeding complications. The severity of these complications is explained by different factors: the inability to perform an efficient compression of the anatomical site, the proximity of a large vessel, the absence of a cutaneous hematoma, which hinders an early detection of a more severe bleeding complication, the delayed onset of neurologic symptoms following the bleed (lumbar block) and the proximity of the spinal cord (paravertebral block).[4] In an analysis of severe hemorrhagic complications, with one death associated with PNB, 18 were associated with coagulation abnormalities and 14 with normal hemostasis.[2]

Most available recommendations classify peripheral nerve blocks according to the potential risk of serious bleeding complications[5]. The risks of bleeding and clinical consequences depend on the location (vicinity of the vessels and critical structures that would be at risk from the mass effect of a hematoma), block depth (which influences needle visibility), body habitus, site compressibility, if bleeding or hematoma is easy or not to assess and how easy or not an intervention may be applied to prevent or treat bleeding, associated comorbidities and anticoagulation status.[2] There are also technical factors such as type and size of the needle used, technical difficulties, multiple attempts, needle passes and bloody tap, use of catheters and type of nerve location technique (USG versus 'blind' techniques), and operator experience.[6,7] In obese patients, structures may lie much deeper than usual, which increases the risk of inadvertent vascular puncture and may hinder effective compression of the bleeding site.

Due to the rare occurrence of bleeding complications and missing data on each specific block (only case reports), a clear risk stratification cannot be performed and current clinical decisions depend mostly on the individual clinician's opinion. To improve clinical decision-making and guidelines application, an expert consensus-based risk assessment of peripheral nerve blocks for bleeding complications was performed (Table 1).[6] For assessment of a bleeding risk, a definition of bleeding complications is necessary. An occurrence of vascular puncture, active bleeding or hematoma formation attributable to a peripheral nerve or interfascial plane block were considered in literature. The risk was assessed based on the following parameters: 1) whether the block is performed in proximity to a critical structure; 2) whether a bleeding complication would potentially require invasive intervention; and 3) whether it would be difficult to assess the severity of the bleeding complication.[6]

Literature on specific blocks:

- *Superficial cervical plexus block:* any bleeding in this area is easily assessable and compressible, and the mass effect of a hematoma in this location would be insignificant.

- *Deep cervical plexus block:* there are no reports of significant bleeding resulting in this block[8]. However, various critical anatomical structures are potentially at risk: vertebral artery, dorsal scapular artery and supra scapular artery.[9] Bleeding from these deeper vessels may be difficult to tamponade non-invasively, and the mass effect from an expanding hematoma in the neck could have significant consequences.

- *Interscalene and supraclavicular block:* there are many arterial structures in the brachial plexus region: the dorsal scapular, transverse cervical, vertebral and subclavian artery. Despite this, there is a low incidence of vascular puncture and bleeding complications during interscalene block (up to 0.63%)[10] and few reported cases of hematoma. Nevertheless, a large expanding hematoma could have serious consequences, including airway compromise.

- *Infraclavicular brachial plexus block:* a risk of vascular puncture of axillary artery, axillary vein and cephalicveinis present, and a reported incidence of vascular puncture was up to 6.6%.[11]

- *Axillary brachial plexus block:* multiple axillary veins and the axillary artery lay adjacent to the nerves of the brachial plexus and increase the risk of axillary hematoma. Nevertheless, the site is readily compressible and, in the past, transarterial technique of axillary brachial plexus blockade was routinely used. Vascular puncture in stimulator-based technique occurred in 8.4% of all performed blocks.[12] In transarterial technique, 0.2% incidence of small hematomas (0–2 cm) was reported.[13]

- *Deep lower limb blocks:* nerves or plexi are situated deep into the skin and close to vital non-compressible structures (kidney, retroperitoneum, pelvic organs). These areas are richly vascularized, not easily compressible in the event of vascular puncture, therefore clinical diagnosis of an expanding hematoma can be difficult. Therefore, lumbar plexus and parasacral sciatic nerve blocks are classified as high risk for bleeding complications. In contrast, blocks far from vital structures (transgluteal sciatic, subgluteal sciatic, anterior sciatic, obturator, and suprainguinal fascia iliaca block) are classified as intermediate risk for bleeding complications. In lumbar plexus block, there were few cases of psoashematoma with lumbar plexopathy, retroperitoneal hematoma and renal subcapsular hematoma. However, the hematoma resolved without invasive intervention or neurologic impairment.[14,15]

- *Superficial lower limb blocks:* if close to large vessels (femoral nerve, femoral triangle, adductor canal, popliteal sciatic nerve), they are considered as intermediate risk, whereas superficial (lateral femoral cutaneous nerve, infrainguinal fascia iliaca and ankle block) are classified as low risk for bleeding complications. The proximity of the femoral artery has led to the occurrence of retroperitoneal hematoma following femoral perineural catheter placement.[16]

- *Other nerve blocks of the lower extremity:* thigh hematoma and pseudoaneurysm of a collateral branch of the superficial femoral artery have been reported after anterior sciatic and adductor canal blocks. The pseudoaneurysm required embolization.[17]

- *Interfascial plane blocks:* although many plane blocks (transversus abdominis plane –TAP, ilioinguinal/iliohypogastric –IIN/IHG, pectoral nerve –PECS, serratus anterior, and the rectus sheath block) are superficial, serious complications such as bleeding, visceral injury and hematoma have been reported in the literature. There are reports of intrapelvic[18] and retroperitoneal hematoma (injury to the deep circumflex iliac artery) [19] with IIN-IHG block and retroperitoneal hematoma with rectus sheath block. After a PECS block, up to 1.6% of patients developed a pectoral hematoma.[20] For the risk of hematoma and visceral injury, above mentioned blocks should be considered as intermediate risk blocks and should be performed using guidance techniques such as ultrasonography by personnel with adequate experience in patients on antithrombotic drugs. According to anatomy, transversalis fascia plane block is considered an intermediate risk block, whereas quadratus lumborum (QL) block is a deeper block with a needle trajectory into a non-compressible space, therefore it is considered a high-risk block. Retrolaminar and erector spinae plane blocks have no critical structures in close proximity, so they are classified as low risk for bleeding complications.

- *Paravertebral block:* the region of the paravertebral space is richly vascular, the lung and major vessels deep to the space additionally contribute to anatomic complexity. Inadvertent vascular puncture was identified in 6.8% of procedures and superficial hematoma requiring external compression, but no invasive procedure in 2.4%.[21] Ultrasound showed no hematomas[22], only some cases of super-

ficial bleeding. Paravertebral blocks are considered by some authors as an escape block if a patient has contraindications for neuraxial procedure. So, paravertebral blocks have been performed in anticoagulated patients: cardiac surgery patients[23], patients with pre-existing coagulopathies[24], thrombocytopenia[25] and antiplatelet medications[26]. No serious complications occurred in any of these reports. Paravertebral space is a non-accessible and non-compressible space, bleeding within the space or into the thoracic cavity is not readily detectable, consequently, paravertebral block is classified as high-risk block.

- *Intercostal block*: a very large series of intercostal blocks were performed without a single bleeding complication[27], even in anticoagulated patients[28]. However, few case reports still warned about the potential life-threatening risks (occult hemothorax).[29] With no critical structures in proximity, it is considered to be an intermediate risk block.

How to approach a patient on antithrombotic therapy

In all patients on antithrombotic drugs, benefits vs. risks should be weighted.

- Low risk PNB: although rare events of bleeding cannot be excluded, they are expected to be easily managed with block performed.
- Intermediate risk PNB: the decision to perform a block should be made on a case-by-case basis. The procedure should be performed by experienced personnel with additional monitoring of the block technique (ultrasound) and potential complications. Blocks should be performed in awake patients (preoperatively) and patients should be monitored for any bleeding manifestations for a prolonged time.
- High risk PNB: the bleeding complications may be associated with significant morbidity or difficult to detect. These blocks should be avoided in patients with elevated bleeding risk except when the benefits clearly outweigh the increased complication risk.
- Weak indication for PNB – PNB provides better comfort and less pain after surgery.
- Strong indication for PNB – PNB causes less postoperative morbidities than general anesthesia.
- Vital indication for PNB – PNB will reduce mortality compared to general anesthesia.

Prevention of hematomas

Current recommendations in regional anesthesia are directed towards prevention of bleeding complications. In majority of patients, bleeding risk should be minimized with the optimization of patient's coagulation, considering appropriate antithrombotic drug timing before regional anesthesia procedure, the dose of antithrombotic drug, indication for the drug and the presence of risk factors that may influence drug pharmacokinetics (bodyweight, age, renal and hepatic function and the concomitant use of other drugs). The optimal duration of antithrombotic drug before PNB in the shortest duration reduces the excess risk of bleeding associated with the drug.

Considering the risk of bleeding complications in individual regional anesthesia procedures, **superficial nerve procedures** may be performed in the presence of antithrombotic drugs, irrespective of the dose (low or high). No routine testing of laboratory values is suggested for superficial nerve procedures, even in high doses. Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point.

Intermediate and high risk (deep) peripheral nerve blocks should be performed according to the recommendations for neuraxial procedures.[4] In general, there are no randomized controlled trials investigating the influence of different doses of antithrombotic drugs on the occurrence of neuraxial anesthesia-related spinal or deep nerve block hematoma in perioperative patients. Consequently, the recommended therapy-free interval of those drugs is, therefore, based on their biological half-lives and when it is not possible to wait, normal values of appropriate laboratory assays (Table 3).[30,31]

With the **combination of antithrombotic drugs,** the therapy-free time interval should be that of the drug with the longest interval. In the postoperative period patients often receive non-steroidal anti-inflammatory drugs (NSAIDs) in combination with unfractionated heparin, low molecular weight heparin or oral anticoagulants, which increases the frequency of spontaneous hemorrhagic complications, bleeding at puncture sites and spinal hematoma.[2]

Presence of an indwelling neuraxial or deep nerve catheter: several cases of neuraxial hematoma proved that catheter insertion and removal carry similar

risks.[32] Therefore, the same time intervals should be applied for both procedures. The next dose of vitamin K antagonists (VKA), direct-acting oral anticoagulants (DOACs), high dose of low-molecular weight heparin (LMWH), and high dose of unfractionated heparin (UFH), fondaparinux and P2Y12 inhibitors should be administered only after catheter withdrawal.[33] In patients with in-going epidural analgesia and thromboprophylaxis, the administration of a non-selective NSAID is contraindicated. Chelly et al.[34] removed femoral, sciatic or lumbar plexus catheters after total knee or hip arthroplasty in 766 patients without any consideration for the timing of the postoperative low dose rivaroxaban and found local puncture site bleeding in only 10 patients. On the other hand, a thigh hematoma with severe motor and sensory deficits of femoral nerve, large retroperitoneal hematoma and hemothorax were described.[3] In *urgent administration of combinations of antithrombotics with a deep nerve catheter already in situ* an interdisciplinary management is suggested, together with laboratory drug measurements and neurological monitoring. With loading doses of aspirin and clopidogrel, a catheter could be removed immediately, before the clopidogrel reaches full effect.

A vessel puncture with a bloody tap increases the risk of bleeding complications, including a hematoma. Also, multiple failed attempts may increase the risk. Consequently, the time interval until the next drug dose, based on an interdisciplinary clinical judgment of the patient's thrombotic risk, the presence of perioperative coagulopathies, the adequacy of postoperative hemostasis and pharmacological profile of the antithrombotic drug, should be increased. The evidence for this is low, however, some experts recommend a delay of an administration of UFH after bloody tap for 1–2h.[35]

Timing and drug monitoring: do laboratory threshold values of antithrombotic drugs reduce the bleeding risk? There are no controlled studies in patients on any antithrombotic drug for single shot blocks or catheter insertions/removals. It is also not known whether drug plasma values have any influence on the rate of wound hematoma after deep or superficial nerve blocks.

On the other hand, laboratory threshold values of antithrombotic drugs may shorten or increase the time interval after drug administration. Targets for neuraxial and deep nerve procedures, irrespective of the time the drug is withheld:

- VKA: a normal INR
- high-dose LMWH or fondaparinux: an anti-Xa activity of 0.1 IU/mL or less, the measurement is predominantly advised in the presence of renal insufficiency (CrCl <30 ml/min) and in older, frail or very low body weight patients[36]
- direct Xa inhibitors: calibrated DXA levels <30 ng/mL or anti-Xa activity ≤ 0.1 IU/mL, advised in renal insufficiency and when the time of last dose is uncertain
- high doses of dabigatran: a thrombintime (TT) within the normal range or a dabigatran level <30 ng/mL, advised in renal insufficiency
- a normal platelet count and/or aggregation test may assist in decision making and shorten the time interval for clopidogrel towards 5 days. However, the most appropriate test of platelet function remains debated.

Drug reversal: neuraxial or deep nerve procedures may be performed in emergency situations following an individual risk-benefit evaluation once the anticoagulant activity of VKA is fully reversed by prothrombin complex concentrate (PCC) and INR-dependent dose adjusted and combined with vitamin K (10 mg). Similar approach is feasible once the anticoagulant activity of dabigatran is fully reversed by the specific antidote idarucizumab. Nonspecific hemostatic agents (PCC or activated PCC) do not affect time intervals for DOACs.[37] Also, once the anticoagulant activity of UFH is fully reversed by protamine and protamine overdose is avoided, in emergency situations, deep nerve blocks could be performed.

Use of ultrasound (US): although USG can reduce the rate of vascular injection almost eight-fold, operator experience, probe choice and needle-probe alignment are also important, whilst it is recognized that ultrasound is more challenging in deeper nerve blocks.[38] An incidence of vascular puncture was noted to be up to 6.6% with nerve stimulator guidance, while it was 0.7% with ultrasound guidance.[39] The advantage of using ultrasonography to visualize normal and aberrant vessels allows the operator to plan a safer

needle trajectory or to select an alternative approach[40], therefore its usage is recommended in patients on anticoagulants and antiplatelet drugs.[41] However, there is no evidence that ultrasound reduces the incidence of hematoma or postoperative neurological symptoms in patients on anticoagulants.[42]

Ultrasound guidance has no influence on the time interval from last administration of antithrombotic drugs (VKA, DOAC, LMWH, UFH, fondaparinux, aspirin and P2Y12 inhibitors) prior to superficial or deep peripheral nerve blocks or to the next drug dose after the block. The lowest bleeding risk technique should be chosen and performed by an operator with experience in ultrasound guidance.

Thrombocytopenia: paucity of clinical data on bleeding risk of thrombocytopenic patients bases the recommendations on expert consensus opinion. Consequently, it is not possible to give definitive values for a lower limit at which there is an increased risk of hematoma. A count of > 75 × 10^9/L has been proposed as an adequate level for all regional anesthesia procedures when there are no other risk factors.[43, 44] In idiopathic thrombocytopenic purpura and gestational thrombocytopenia, there are reduced platelet numbers, but normal function, therefore an experienced anesthetist might perform a neuraxial blockade, providing that platelet count is > 50 × 10^9/L, but an individual risk-benefit assessment should be made.[45]

Conclusion

Bleeding complications following peripheral nerve blocks are rare, but may lead to significant patient morbidity and need for further investigations and interventions. The risk of bleeding complications depends on the degree of trauma produced by the needle, patient coagulation status and type of the block. The risk of bleeding complications and the subsequent sequelae need to be weighed against the potential benefits on a case-by-case basis. Where the bleeding risk is high, alternative techniques should be considered (general anesthesia or low bleeding risk regional anesthesia techniques, if possible). The paucity of evidence in anticoagulated patients does not necessarily translate into a lower risk of bleeding complications, as most of these blocks will not routinely be offered to such patients, given existing regional anesthesia guidelines.

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Sažetak

BLOKOVI PERIFERNIH ŽIVCA U BOLESNIKA NA ANTITROMBOTICIMA – SPAS ILI NEPOTREBAN RIZIK?

P. Poredoš

Komplikacije krvarenja nakon blokada perifernih živaca (PNB) u bolesnika liječenih antiagregacijskim sredstvom i/ili antikoagulansima su rijetke, procijenjena incidencija je 0,67% (0,51 - 0,83%). Međutim, mogu dovesti do značajnog morbiditeta pacijenata i mogu zahtijevati naknadne pretrage i intervencije. Dokazi o rizicima od krvarenja i komplikacijama nakon PNB-a vrlo su mali ili ih uopće nema, stoga se preporuke i smjernice temelje na retrospektivnim analizama, izvješćima slučajeva, stručnim mišljenjima i konsenzusu stručne skupine. U rukopisu je predstavljen konsenzus stručnog povjerenstva o klasifikaciji PNB-a prema potencijalnom riziku od ozbiljnih komplikacija krvarenja. Rizici od krvarenja ovise o lokaciji (blizina krvnih žila i kritičnih struktura u opasnosti od masovnog učinka hematoma), dubini bloka (koja utječe na vidljivost igle), povezanim komorbiditetima i antikoagulacijskom statusu, tjelesnom habitusu, kompresiji mjesta, ako krvarenje ili hematom je lako ili ne procijeniti i koliko se lako ili ne može primijeniti intervencija za sprječavanje ili liječenje krvarenja. Također, razmatraju se tehnički čimbenici: vrsta i veličina upotrijebljene igle, tehničke poteškoće, višestruki pokušaji, prolasci iglom i krvavo tapkanje, uporaba katetera i vrsta tehnike lociranja živaca (USG u odnosu na ‚slijepe' tehnike), te iskustvo operatera.

U svih bolesnika koji uzimaju antitrombotičke lijekove potrebno je odmjeriti korist i rizik. Rizik od krvarenja treba svesti na najmanju moguću mjeru uz optimizaciju koagulacije bolesnika: odgovarajuće vrijeme antitrombotičkog lijeka prije PNB, doza antitrombotičkog lijeka, indikacija za lijek i čimbenici rizika koji mogu utjecati na farmakokinetiku lijeka (tjelesna težina, dob, bubrežna i jetrena funkcija). Površinski PNB može se izvesti u prisutnosti antitrombotičkog lijeka. Za duboke PNB-ove treba razmotriti preporuke za neuraksijalne postupke.

Ključne riječi: *blokada perifernih živaca, antikoagulansi, inhibitori trombocita, komplikacije krvarenja, regionalna anestezija*

Tables

Table 1 Risk categorization of peripheral nerve blocks (PNB) (Adapted from Ref. 6)

Body region	Block	Consensus	Grade*
Head and neck	Occipital, peribulbar, Sub-tenon's PNB	Low risk	III–B
	Superficial cervical plexus block	Low risk	III–B
	Deep cervical plexus block	High risk	III–B
	Stellate ganglion	High risk	IV–C
Above clavicle	Interscalene brachial plexus block	Intermediate risk	III–C
	Supraclavicular brachial plexus block	Intermediate risk	III–C
Below clavicle	Infraclavicular brachial plexus block	Intermediate risk	III–C
	Axillary brachial plexus block	Low risk	III–C
	Median, radial, ulnar PNB	Low risk	IV–C
Lumbar plexus	Lumbar plexus, psoas compartment b.	High risk	III–B
	Femoral nerve block	Intermediate risk	III–C
	Pericapsular nerve group	Intermediate risk	
	Lateral femoral cutaneous n. block	Low risk	IV–C
	Suprainguinal fascia iliaca block	Intermediate risk	IV–C
	Infrainguinal fascia iliaca block	Low risk	IV–C
	Obturator nerve block	Intermediate risk	IV–C
	Adductor canal nerve block	Intermediate risk	IV–C
Sacral plexus	Proximal sciatic nerve block (anterior, transgluteal, subgluteal)	Intermediate risk	IV–C
	Popliteal sciatic nerve block	Intermediate risk	IV–C
Ankle	Ankle block	Low risk	IV–C
Interfascial plane	Rectus sheath	Intermediate risk	III–C
	TAP block	Intermediate risk	III–C
	TAP subcostal block	Intermediate risk	IV–C
	Ilioinguinal/Iliohypogastric block	Intermediate risk	III–C
	Quadratus lumborum block	High risk	IV–C
	Transversalis fascia block	Intermediate risk	IV–C
	Erector spinae plane block	Low risk	IV–C
	PECS 1	Intermediate risk	III–C
	PECS 2	Intermediate risk	IV–C
	Serratus anterior plane block	Intermediate risk	IV–C
Truncal	Paravertebral	High risk	III–B
	Intercostal	Intermediate risk	III–C

PNB – peripheral nerve block, TAP – transverse abdominis plane, PECS – pectoralis nerve

*Grade of recommendation

Table 2 Management of antithrombotic therapy in superficial PNBs (adapted from Ref. 30)

Drug and dose	Time from last antithrombotic drug intake to PNB	Time from PNB to next antithrombotic drug dose
Direct Xa antagonist Direct thrombin inhibitor LMWH low and high* UFH low and high* Fondaparinux Aspirin VKA* $P2Y_{12}$ inhibitor	0	Routinely prescribed next time point

LMWH – low molecular weight heparin, UFH – unfractionated heparin, VKA – vitamin K-antagonist

*Within or below therapeutic range

Table 3 Management of antithrombotic therapy in deep PNBs (adapted from Ref. 30)

Drug and dose	Time from last drug intake to PNB	Target laboratory value at PNB	Time from PNB to next drug dose
VKA	Target lab. value (warfarin 5 days)	INR normal	
DXA low	24h rivaroxaban, 36h apixaban	/	
DXA high	72h or until target lab value	DXA < 30 ng/mL (alternative: anti-Xa ≤ 0.1 IU/mL)	Low dose: 8h
Dabigatran low	48h	/	
Dabigatran high	72h or until target lab value	DTI level < 30 ng/mL (alternative: thrombin time)	24h
LMWH low	12h (24h if CrCl<30)	/	2-6h
LMWH high	24h (48h if CrCl<30) or until target lab value	anti-Xa ≤ 0.1 IU/mL	2-6h
UFH low	4h	/	1h
UFH high	Until target lab value (6h i.v., 12h s.c.)	aPTT or anti-Xa or ACT normal	6h
Fondaparinux low	36h (72h if CrCl<50)	/	6h
Fondaparinux high	Until target lab value (4 days)	calibrated anti-Xa ≤ 0.1 IU/mL	
Aspirin low	0	/	Routinely
Aspirin high	3 days (normal platelet count)	normal platelet function tests	6h
$P2Y_{12}$ inhibitor	5 days ticagrelor 5-7 days clopidogrel 7 days prasugrel		0h clopidogrel 75 mg 24h prasugrel, ticagrelor 2 days clopidogrel 300 mg
GPIIb/IIIa	24-48h abciximab 4-12h eptifibatide 8-12h tirofiban		24h
Dypiridamole	12h		0
Aspirin low + anticoagulant	Aspirin 0 + time interval of specific anticoagulant	Specific lab. tests for anticoagulant	Aspirin routinely, anticoagulant according to guidelines
Aspirin low + antiplatelet drug	Aspirin 0 + time interval of specific antiplatelet drug	Specific lab. tests for antiplatelet	

ACT – activated clotting time, aPTT – activated partial thromboplastin time, CrCl – creatinine clearance, DTI – direct thrombin inhibitor, DXA – direct Xa antagonist, GP – glycoprotein, INR – international normalized ratio, LMWH – low molecular weight heparin, UFH – unfractionated heparin, VKA – vitamin K antagonist