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SCIENTIFIC ARTICLE

SBA Recommendations for regional anesthesia safety in patients taking anticoagulants

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Description of evidence collection method

We conducted searches in multiple databases (Medline 1965-2012; Cochrane Library, Lilacs) and cross-references with the collected material to identify studies with better methodological design, followed by a critical evaluation of their contents and classification according to the strength of evidence.

We conducted searches between August and December 2012. The following strategies were used for searches in PubMed:

1. "regional anaesthesia" OR "anesthesia, conduction" OR "anesthesia" AND "conduction" OR "conduction anesthesia" OR "regional" AND "anesthesia" OR "regional anesthesia" AND "antithrombotic";
2. "regional anaesthesia" OR "anesthesia, conduction" [MeSH Terms] AND "infection" [MeSH Terms] AND "thromboembolism" [MeSH Terms] OR "thromboembolism" [All Fields];
3. "thromboembolism" [MeSH Terms] OR "thromboembolism" [All Fields] AND "regional anaesthesia" [All Fields] OR "anesthesia, conduction" [MeSH Terms] OR "anesthesia" [All Fields] AND "conduction"

[All Fields]) OR "conduction anesthesia" [All Fields] OR "regional" [All Fields] AND "anesthesia" [All Fields] OR "regional anesthesia" [All Fields].

In the field of regional anesthesia, we selected studies addressing managements of different types of regional anesthesia in individuals taking drugs that modify the blood coagulation status. We focused on risk factors, etiology, prevention, diagnosis, and treatment. We also included studies assessing the risk of complications in patients after regional blockade and studies that clarify the management and safe handling of drugs to be administered.

Level of evidence and strength of recommendation

- A: Experimental or observational studies with better consistency.
- B: Experimental or observational studies with less consistency.
- C: Case reports or case series (non-controlled studies).
- D: Opinion without critical evaluation, based on consensus, expert opinions, physiological studies, or animal models.

Objective

To assess the safety aspects of regional anesthesia and analgesia, such as the possible technique's complications;

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risk factors associated with spinal hematoma, prevention strategies, diagnosis, and treatment; and safe interval for drug suspension and resumption after regional block in patients taking antithrombotic drugs.

Introduction

The current incidence of neurological dysfunction resulting from bleeding complications associated with neuraxial block is unknown.¹ Its occurrence is estimated to be less than 1:150,000 epidural punctures and 1:220,000 subarachnoid punctures.¹ After neuraxial anesthesia, the use of anticoagulants is the risk factor most often associated with spinal hematoma.² Because spinal hematoma is rare, recommendations regarding regional anesthesia and concomitant use of thromboprophylaxis or antithrombotic therapy, which would be of greater predictive value if reported by prospective randomized studies, are based on case reports and expert recommendations³, which ethically precludes the study.

The number of patients on anticoagulant therapy has been growing due to the aging process, longer life expectancy, and prevalence of cardiovascular disease. Recommendations on safety in regional anesthesia and antithrombotic therapy should be constantly updated, as the introduction of new antithrombotic drugs to the market is done at regular intervals.²

This guideline aims to review the risks and recommendations for regional anesthesia in subjects taking drugs that interfere with coagulation and present safety regulations and guidelines required for regional procedures.

Spinal/epidural hematoma

Incidence

Although the incidence of spinal-epidural hematoma (SEH) is small, the clinical severity of its consequences, along with litigation costs that follow an adverse event, makes it crucial to develop sound strategies for the management of patients on anticoagulants during neuraxial anesthesia.⁴

In a literature review⁵ assessing several case reports, we noted that the incidence of SEH was 1:220,000 after spinal anesthesia and 1:150,000 after epidural puncture. However, recent indications suggest a higher incidence, as the studies used in these calculations were conducted before the perioperative thromboprophylaxis routine.⁶

After the introduction of enoxaparin (30 mg, twice daily) for thromboprophylaxis in the United States, an alarming number of cases of epidural hematoma, some with permanent paraplegia, the risk of spinal/epidural hematoma with twice daily administration of enoxaparin was reported and calculated at 1:40,800 after spinal anesthesia, 1:6,600 after simple epidural puncture, and 1:3,100 after epidural puncture with epidural catheter insertion.⁷ In Europe, a single dose administration of enoxaparin (40 mg) showed a lower incidence of spinal hematoma. In a retrospective Swedish study,⁸ the authors found a risk of 1:156,000 after spinal anesthesia and 1:18,000 in epidural anesthesia. Bleeding was rare in the obstetric population (1:200,000) compared with that of women undergoing knee arthroplasty (1:3,600).

Subsequent studies showed incidences as high as 1:2,700 to 1:19,505.⁹⁻¹¹ However, Cook et al. presented updated results at the Third National Audit Project of the Royal College of Anaesthetists in which only eight cases of SEH were seen in 707,405 neuraxial blocks. Of these, only five met the inclusion criteria, and the incidence was calculated at 1:88,000 to 1:140,000.¹²

Risk Factors^{2,4}

The occurrence of SEH is more spontaneous than the result of neuraxial anesthesia. Most spontaneous hematomas are idiopathic; cases related to anticoagulant therapy and vascular malformations are the second and third most common causes, respectively. Concomitant use of anticoagulants is the main risk factor related to SEH, when associated with neuraxial block.²

Risk factors for SEH have been described by several authors^{8,13-18} and are shown in Table 1. The incidence of SEH varies according to the type of surgery, age and gender of patient. For example, the incidence of SEH in obstetric surgery is estimated at 1:200,000, whereas in geriatric age women undergoing knee arthroplasty it is estimated at 1:3,600.⁸ This may be explained by the higher incidence of spinal abnormalities associated with osteoporosis, use of dual antiplatelet/anticoagulant therapy, and accumulation of anticoagulant due to a decrease in renal excretion not detected in this age group.

Among the type of neuraxial blocks, the risk of SEH is higher with the use of epidural catheters, followed by simple epidural puncture, and less frequent after single subarachnoid puncture,^{17,19,20} the latter likely due to the thinner needles used in the technique. Catheter removal is as critical as insertion; therefore, vascular injury may still occur⁴ at the same incidence; that is, half the cases of SEH occurs during epidural catheter removal.¹⁶

There are indications that epidural hematoma is more common after lumbar puncture compared with thoracic puncture.¹¹

Clinical condition, treatment, and prevention

Bleeding into the spinal canal, which causes thecal sac compression, may result in irreversible neurological damage with paraplegia and is a major concern of anesthesiologists performing neuraxial block in patients on anticoagulant drugs.⁴

Clinical condition is characterized by slow regression or absent sensory or motor block, back pain, urinary retention or return of motor or sensory deficit after complete regression of the previous block, alone or in combination, suggesting the development of spinal hematoma.²

In the presence of clinical suspicion of spinal hematoma, an aggressive diagnostic and therapeutic approach is mandatory. This includes emergency nuclear magnetic resonance imaging (NMRI) or, if unavailable, computed tomography (CT). Because SEH is a neurosurgical emergency, protocols must be established to avoid any delay in diagnosis. Once diagnosis is confirmed, decompressive laminectomy should be performed within 6-12 hours after the onset of symptoms, enabling chances of neurological recovery.^{16,21}

Table 1 Risk Factors Associated with Hematoma Spinal/Epidural.

- 1 – Patient-related
- Age (elderly);
 - Female;
 - Congenital coagulopathies;
 - Acquired coagulopathies (renal/hepatic malignancies, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), disseminated intravascular coagulation [DIC]);
 - Thrombocytopenia;
 - Spinal abnormalities (spina bifi da/spinal stenosis, osteoporosis, ankylosing spondylitis).
- 2 – Procedure-related
- Insertion or removal of the catheter;
 - Traumatic procedure (multiple attempts);
 - Presence of blood in the catheter during insertion or removal;
 - Epidural catheter insertion > Simple epidural puncture > Simple spinal puncture.
- 3 – Drug-related
- Anticoagulant drugs, antiplatelet or fibrinolytic;
 - Administration of the drug immediately before/after neuraxial technique;
 - Use of antiplatelet therapy/dual anticoagulant.

Drugs	Recommendations
ASA and NSAIDs	There is no indication of suspension.
ASA and NSAIDs + LMWH/UFH/coumarin	Wait 24 hours for neuraxial block or epidural catheter insertion.
ASA + thienopyridine	If the patient is using metallic stent, wait 6 weeks. If the stent is pharmacological, wait 6 months.
Ticlopidine	Perform blockade or insertion/removal of catheter 10-14 days after suspension.
Clopidogrel	Perform blockade or insertion/removal of catheter 7 days after suspension. In high risk patients, it may be performed in 5 days.
Prasugrel	Perform neuraxial block 7-10 days after drug discontinuation.
Abciximab	Perform neuraxial block or insertion/removal of catheter 48 hours after drug discontinuation.
Tirofiban/efitibatide	Wait 8-10 hours to perform neuraxial block or epidural catheter insertion.
Glycoprotein IIb/IIIa inhibitors + other anticoagulants/AAS	Contraindication for blockade.
Ticagrelor	Perform blockade or insertion/removal of catheter 5 days after drug discontinuation.
Cilostazol	Perform blockade or insertion/removal of catheter 5 days after drug discontinuation.
Unfractionated heparin	Wait 4 hours after the last dose of UFH for blockade, removal/insertion of catheter. Restart drug after 1 hour.

Table 1 (Continued)

Drugs	Recommendations
Low molecular weight heparin	Prophylactic doses: wait 10-12 hours to perform blockade. Therapeutic doses: wait 24 hours. Withdrawal of catheter 10-12 hours after last dose. Restart drug 2 hours after catheter removal.
Coumarin	Perform blockade 4-5 days after discontinuation. INR monitoring during epidural analgesia.
Fondaparinux	Prophylactic dose (2.5 mg): blockade may be performed. If epidural catheter, remove it 36 hours after the last dose. Restart dose 12 hours after catheter removal. Therapeutic dose (5-10 mg): blockade is contraindicated.
Rivaroxaban	Perform neuraxial blockade, insertion/removal of catheter 24 hours after drug discontinuation. Restart 4-6 hours after catheter removal.
Apixaban	Perform neuraxial blockade, insertion/removal of catheter 20-30 hours after drug discontinuation. Restart 4-6 hours after catheter removal.
Desirudin	Perform blockade 8-10 hours after drug discontinuation in patients with normal renal function.

Thus, patients should be carefully evaluated to investigate possible signs indicating SEH, both after neuraxial block and epidural catheter removal. The patient should be monitored at regular intervals until regression of sensory block by at least two dermatomes or motor function recovery² and for at least 24 hours after epidural catheter removal.²¹

European and American societies have published guidelines with the goal of increasing security in performing neuraxial block in patients on anticoagulants.^{1,6,22-27} However, most of these recommendations are expert opinions based on case series and pharmacological data with anticoagulant drugs involved.²⁷ These recommendations include: (I) minimum time interval required between the last dose of anticoagulant and the insertion of neuraxial needle/catheter or catheter removal; (II) minimum interval required between the insertion of neuraxial needle/catheter or catheter removal and next dose of anticoagulant; (III) minimum coagulation time required for the use of neuraxial technique (if available for the drug being used).

Due to the rapid development of anticoagulant drugs by the pharmaceutical industry and their release and increasing use in clinical practice, experiments are lacking and it becomes difficult to make any statement on the use of neuraxial anesthesia in patients on new anticoagulants.

Recently, Rosencher et al. proposed a new strategy for managing patients on new anticoagulants.²⁸ According to this strategy, the insertion and subsequent withdrawal of neuraxial needle/catheter must be made at a time superior to two half-lives of elimination after the last dose of the used anticoagulant. The basis for this proposal is that 30% to 40% of the function of coagulation factors is required for hemostasis, so that after two half-lives, the drug concentration in bloodstream is near 25% of the initial. The next anticoagulant dose should be administered with a time interval (dT) obtained by subtracting the time needed for the drug to reach the peak plasma level and the time to produce stable blood clot, considered 8 hours ($8h - T_{\text{peak}} = dT$).²⁸

Neuraxial block and use of antiplatelet agents

Antiplatelet drugs consist of non-steroidal anti-inflammatory drugs (NSAIDs), thienopyridines (ticlopidine, clopidogrel, and prasugrel), and glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban).

Acetylsalicylic acid (ASA) and NSAIDs

ASA promotes irreversible blockade of platelet function by inhibiting cyclooxygenase enzyme production of thromboxane A₂ (potent platelet activator). This effect lasts the same as the platelets' half-life, usually 7-10 days.³

Other NSAIDs also inhibit cyclooxygenase-1 and platelet aggregation, but in a reversible manner and proportional to the agent half-life. This process normalizes from 12 to 24 hours after NSAIDs discontinuation.²⁹ The selective inhibitors of Type 2 cyclooxygenase (COX-2) are anti-inflammatory drugs that do not cause platelet dysfunction, as COX-2 is not expressed in platelets.³⁰

The bleeding effect caused by ASA appears to be dose-dependent, with more marked effects in patients receiving

doses greater than 100mg.day⁻¹.³¹ However, prospective studies evaluating the safety of neuraxial block with ASA reported no case of spinal hematoma.³²⁻³⁴

Although the isolated use of ASA seems not to increase the probability of spinal hematoma, complications have been observed in both medical and surgical patients, if combined with heparin.^{14,35} Thus, in individuals using ASA, it seems prudent to administer heparin for postoperative thrombosis prophylaxis, as the research team did not observe superiority of thromboprophylaxis when the heparin dose is given preoperatively (B).³⁶ However, the administration of a low-dose combination of ASA-dipyridamole seems not to increase the risk of spinal hematoma.²

In patients with a history of acute coronary syndrome (ACS), cerebrovascular accident (CVA) or peripheral arterial occlusive disease, ASA reduces the risk of recurrent cardiovascular events by 30% and mortality by approximately 15%.³⁷ Recent studies suggest that morbidity and mortality, particularly in patients with newly implanted coronary stents or unstable coronary syndrome is markedly increased if ASA is suspended before a surgical procedure.³⁸⁻⁴⁰ Rebound phenomenon has also been described.⁴¹ The risk of late thrombosis is higher in patients with drug-eluting stents.

In summary, the perioperative suspension of ASA is unnecessary in most cases and associated with an increased risk of acute thrombosis. We recommend that patients with ACS or stent should continue taking ASA throughout life.⁴² The American College of Chest Physicians (ACCP) does not recommend platelet function evaluation prior to invasive procedures because there is no apparent correlation with bleeding (D).⁴³

Recommendations

1. NSAIDs appear to represent no significant additional risk for the onset of spinal hematoma in patients undergoing epidural or spinal anesthesia. NSAIDs (including ASA) have no risk level that interferes with the performance of neuraxial blocks. In patients on these medications, there is no specific concern regarding the interval between spinal/epidural puncture or catheter insertion and the last dose of the given drug, or the need for postoperative monitoring and interval for catheter removal or postoperative drug administration (A).^{6,32-34}
2. Concomitant use of medications affecting other clotting mechanism components, such as oral anticoagulants, unfractionated or low molecular weight heparin increases the risk of bleeding complications in patients on NSAIDs. In these patients on ASA, the administration of heparin dosage for postoperative thromboprophylaxis is recommended (B).³⁶ In these patients, if low molecular weight heparin (LMWH) is administered preoperatively, there should be a 24-hour wait period before performing blockade or removing the epidural catheter due to the increased risk of bleeding (C).⁶
3. Cyclooxygenase Type 2 inhibitors (COX-2) have minimal effect on platelet function and should be preferred in patients who need anti-inflammatory therapy in the presence of anticoagulation (D).⁶ There is no evidence

supporting the effect on the ability of platelet aggregation or increased tendency to bleeding (D).¹

4. In patients with coronary stent receiving dual platelet therapy (ASA + thienopyridine), needing surgery, and requiring surgical procedure, we recommend postponing surgery for at least 6 weeks in the case of metallic stents and at least 6 months in case of drug-eluting stents (D).⁴³ If patients need surgery within 6 weeks after metallic stent or 6 months after drug-eluting stent, dual antiplatelet therapy should be maintained, and regional anesthesia is contraindicated via neuraxial route (D).⁴³
5. Analgesics, such as paracetamol and dipyron, are not a contraindication for neuraxial regional anesthesia, insofar there are no cases related to spinal hematoma (D).³

Thienopyridines

Ticlopidine (Ticlid®), clopidogrel (Plavix®), and prasugrel (Efient®) are platelet inhibitors belonging to the class of thienopyridines. They are prodrugs cleaved in vivo in the liver to active metabolites that antagonize the platelet receptor of adenosine dinucleotide phosphate (ADP) (P2Y12) and interfere with platelet activation and aggregation, an effect that can not be antagonized and is irreversible.^{1,2}

There is no prospective study assessing the safety of neuraxial techniques in subjects under treatment with thienopyridines. However, cases of spinal hematoma have been reported after neuraxial anesthesia in patients taking these drugs.⁴⁴

Ticlopidine (Ticlid®)

Ticlopidine half-life is 30 to 50 hours, which increases up to 96 hours if used routinely for more than 14 days.² Platelet dysfunction with the use of ticlopidine remains for 10 to 14 days after drug discontinuation.¹ Unlike clopidogrel, ticlopidine may lead to neutropenia in more than 1% of patients, which is a limiting factor of its use.³

Recommendations

Neuraxial block or epidural catheter removal can only be performed after 10-14 days of ticlopidine suspension (D).^{3,6}

Clopidogrel (Plavix®)

Clopidogrel half-life is 120 hours. However, its active metabolite half-life is only 8 hours.² The platelet function maximum inhibition of oral clopidogrel (75 mg) occurs within 3-7 days or about 12-24 hours after an initial loading dose of 300-600 mg. Recovery of platelet function occurs only 6-7 days after the end of clopidogrel administration.⁴⁵ In patients at high risk for angina, discontinuation for five days has been suggested to prevent cardiovascular morbidity.⁴⁶

Recommendations

Neuraxial blockade or removal of epidural catheter in patients on clopidogrel should only be performed after at least seven days of drug discontinuation (D).³ In the case of

patients with high risk of angina recurrence, the interval of five days suspension has been suggested (D).⁶

Prasugrel (Efient®)

A novel thienopyridine that, similar to others, depends on hepatic conversion to active metabolite to bind to platelet P2Y12 receptor (which binds to ADP for platelet activation) and perform its inhibitory activity. This drug has a rapid onset of action (30-60 minutes) and is 10 times more potent than clopidogrel.⁴⁷ The antiplatelet effect is equal to the life of platelet, and pretreatment platelet function is restored 7-10 days after drug discontinuation.³

One study comparing prasugrel and clopidogrel in 13,608 patients with acute coronary syndrome undergoing percutaneous coronary intervention showed significant reduction of ischemic events treated with prasugrel, but also a higher and occasionally fatal risk of bleeding.⁴⁸

Recommendations

There is no available study assessing the combination of prasugrel and neuraxial anesthesia. However, it seems reasonable that treatment with prasugrel be discontinued at least 7-10 days before neuraxial block or removal of epidural catheter (D).³

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors include abciximab (Reopro®), eptifibatide (Integrilin®), and tirofiban (Aggrastat®). Currently, these agents are the most effective drugs available for platelet aggregation inhibition, as they block the platelet glycoprotein IIb/IIIa (the site of fibrinogen binding between platelets), which is the final common pathway of platelet aggregation.² These drugs are only available for intravenous use. Antiplatelet effects are reversible and disappear after the discontinuation of eptifibatide, tirofiban, and abciximab within 8, 24, and 48 hours, respectively. The most common side effects are thrombocytopenia and bleeding,⁵⁰ expressed in 0.3-1% with abciximab.⁴⁹ Abciximab showed better efficacy than tirofiban and eptifibatide.⁵¹

Recommendations

1. According to the pharmacological properties of these drugs, insertion of epidural/spinal needle/catheter or catheter removal should only be performed after complete recovery of platelet aggregation; that is, with discontinuation of 8-10 hours for tirofiban/eptifibatide and 48 hours for abciximab and exclusion of any thrombocytopenia through a recent platelet count (D).²
2. GP IIb/IIIa inhibitors are used in acute coronary syndrome, in combination with anticoagulants and ASA. In this scenario, any neuraxial blockade is contraindicated in emergency procedures that usually involve cardiac surgery with continued anticoagulation (D).³

Other antiplatelet

Ticagrelor (Brilinta®)

Unlike thienopyridines, ticagrelor acts directly on P2Y₁₂ receptor and does not require liver biotransformation into active metabolites by cytochrome P450, although metabolites are also active. Similar to prasugrel, ticagrelor provides a very fast (< 2h), intense (about 70%), and consistent inhibition of P2Y₁₂ receptor, which is greater than that of clopidogrel (30-40%).⁴⁷ It has a rapid onset of action with reversible binding and short duration (48-72h), and requires oral administration in two doses. The initial effect on platelet aggregation is seen 30 minutes after loading dose. With treatment discontinuation, platelet function is restored within 4-5 days.⁵²

Recommendations

There is no available data regarding the perioperative use of this agent. Theoretically, its short and reversible antiplatelet effect can facilitate perioperative management. However, neuraxial anesthesia should be discouraged during treatment with ticagrelor, unless it is suspended for at least five days before the anesthetic procedure, so that platelet function can return to normal (D).³

Cilostazol (Vasogard®, Cebralat®, Pletal®)

Cilostazol provides selective inhibition of phosphodiesterase IIIa (PDEIIIa); thus, it increases the level of intracellular cyclic adenosine monophosphate (cAMP) and leads to weak platelet aggregation inhibition.^{53,54} Because vascular smooth muscle contains PDEIIIa, cilostazol also provides direct arterial vasodilation. Nevertheless, cilostazol mechanism of action is not fully understood. Its use is indicated for peripheral arterial disease and intermittent claudication in individuals who do not respond to exercise therapy and those with low possibility of surgical intervention.⁵⁵

The route of administration is orally at a dose of 100 mg twice daily, and peak plasma level is achieved within 2.7 to 3.6 hours. Drug compound is mainly eliminated by hepatic metabolism and subsequent urinary excretion of metabolites. The terminal elimination half-life of cilostazol and its active metabolites is approximately 21 hours, and some of its metabolites inhibit platelet aggregation at a higher intensity than the parent compound.⁵⁴

A recent case report found spinal hematoma after epidural catheter removal during treatment with cilostazol,⁵⁶ but, in general, there is no prospective data on this drug's perioperative use and its effect on bleeding incidence is unknown.

Recommendations

Neuraxial block and catheter removal may be performed considering the minimum clearance interval of two half-lives between blockade and the last dose of cilostazol (i.e., 42 hours), although laboratory recommendation is five days of suspension.³ The next dose of cilostazol should only be administered 5 hours after catheter removal (D).^{28,57}

Heparins

Unfractionated heparin (UFH)

The major anticoagulant effect of heparin is due to pentasaccharide present in one third of heparin molecules, which binds to antithrombin III (ATIII).⁶ After this binding, UFH catalyses the inactivation of IIa (thrombin), IXa, and Xa, and, to a lesser extent, XIa and XIIa factors.⁴ In the absence of heparin, antithrombin III has low affinity for thrombin. However, when UFH binds to ATIII, the thrombin-binding rate accelerates from 100 to 1,000 times, similarly to other coagulation factors inhibited by it. UFH also binds strongly to several plasma proteins, endothelial cells, macrophages, and platelet factor 4 (PF4), which results in low bioavailability, inaccurate pharmacokinetics, and heparin-induced thrombocytopenia (HIT).⁵⁸

The anticoagulant activity of UFH depends on both the number of heparin molecules with the pentasaccharide chain in its composition and the size of molecules containing the pentasaccharide. The high molecular weight heparins will catalyze the inhibition of Xa and IIa factors, while the low molecular weight heparins will only inhibit the Xa factor.^{58,59}

Intravenous administration of UFH results in immediate anticoagulation, while subcutaneous administration results in onset of action within 1-2 hours. The anticoagulant effect is both molecular weight and dose dependent, in a non-linear manner, and increases disproportionately with increased dose.⁶ The biological half-life of heparin increases from 30 minutes with 25 UI.kg⁻¹ IV to 60 minutes with 100 UI.kg⁻¹ and to 150 minutes with 400 UI.kg⁻¹.⁵⁹

When given in therapeutic doses, UFH anticoagulation is monitored by the activated partial thromboplastin time (aPTT). During cardiopulmonary bypass, coagulation inhibition by high doses of heparin is monitored by the activated clotting time (ACT). Subcutaneous administration of small doses (5,000 IU) for prophylaxis of deep venous thrombosis (DVT) usually does not change the aPTT. One of the advantages of heparin anticoagulation is the reversal by protamine. Each milligram of protamine can neutralize 100 IU of heparin.⁵⁸

A review study of more than 9,000 patients undergoing neuraxial block with prophylactic doses for DVT with heparin showed no cases of spinal hematoma.⁶⁰ However, isolated cases have been reported subsequently to that revision.^{9,16,10,61-63} In patients receiving two- daily dose regimen of subcutaneous UFH (5,000 IU) there is no contraindication for the use of neuraxial techniques.⁶ However, there are insufficient data to confirm the safety of neuraxial techniques with three daily doses, despite being the most effective dosage for DVT prevention.⁶⁴

In contrast to UFH prophylactic regimen, anticoagulation therapy is definitely associated with increased risk of spinal hematoma.⁴ A prospective study (n=342) comparing the incidence of spinal hematoma in patients with and without therapeutic doses of UFH and undergoing lumbar puncture showed incidence of 2% in the UFH group. The risk factors were: (i) less than 1 hour interval between the onset of heparin and lumbar puncture; (ii) concomitant use of ASA at the time of lumbar puncture; and (iii) traumatic procedure.¹⁴

Recently, two cases of epidural hematoma were reported associated with UFH therapy and neuraxial block.^{65,66}

Heparinization during surgery involves the use of 5,000 to 10,000 U of heparin intravenously during surgery, particularly in vascular surgery to prevent thrombosis during artery clamping.⁵⁹ Most published cases series uses the same guidelines for neuraxial anesthesia management in these patients, based on the exclusion of high-risk patients (preexisting coagulopathy) and performing the neuraxial technique at least one hour before heparin administration.⁶⁰ Stafford-Smith showed increased incidence of bleeding in patients on ASA associated with intraoperative intravenous heparin. SEH risk increased to 1:8,500 after epidural puncture and to 1:12,000 after spinal anesthesia, even when neuraxial anesthesia and subsequent heparinization occurred after one-hour interval.³⁵

In cardiac surgery, the benefits of thoracic epidural anesthesia on pulmonary function and analgesia are evident, with lower intensity for arrhythmia management and no effect on hospital and ICU length of stay and mortality.^{67,68} However, the benefits must be evaluated concerning the high risk of SEH. The probability of spinal hematoma in patients undergoing cardiac surgery with full heparinization is 1:1,528 with epidural and 1:3,610 with spinal techniques.^{69,70} Experts recommend that neuraxial block be performed the day before surgery due to complete surgical heparinization.^{22,71,72} Because neuraxial blockade in cardiac surgery carries significant risks without improving morbidity and mortality, there is discussion whether epidural or spinal anesthesia is justified, probably with the contraindication of the technique in this group.⁷²

Recommendations

1. In patients on two daily prophylactic doses of UFH (5,000 IU) there are no contraindications to neuraxial block (D);⁶
2. The safety of neuraxial block in patients receiving prophylactic doses of UFH above 10,000 IU or above two daily doses is not established. Although dosage of three daily doses may lead to increased surgical bleeding, it is unclear whether there is an increased risk for spinal hematoma development (D);⁶
3. Because heparin-induced thrombocytopenia (HIT) may occur during UFH administration, platelet count should be done before neuraxial technique or catheter removal, if the patient is on HNF for five or more days (B);³
4. Wait a minimum interval of 4 hours between the last prophylactic dose of UFH and spinal/epidural puncture or epidural catheter removal. The next dose of prophylactic UFH should be administered at least one hour after neuraxial anesthesia or epidural catheter removal (D);³
5. If UFH is used in therapeutic doses to perform neuraxial anesthesia, administration of continuous intravenous heparin therapy should be discontinued for at least 4 hours before puncture or catheter removal, and it is necessary to check the return of normal coagulation by determining aPTT or ACT (D);³
6. In situations of intraoperative heparinization, the following recommendations should be considered: 1) minimum interval of one-hour between puncture or catheter placement and heparinization; 2) do not perform neuraxial

block in patients with coagulopathy or on anticoagulants; 3) wait 4 hours between the last dose and epidural catheter removal, preferably with laboratory coagulation tests; 4) after catheter removal, wait one hour for UFH dose application; 5) although the occurrence of difficult puncture or blood output from puncture needle may increase the risk of spinal hematoma, there are no data to justify surgery cancellation (A).⁶

Low molecular weight heparin (LMWH)

LMWH has become the treatment of choice for both prevention and treatment of DVT, due to the greater bioavailability (almost 100%) after subcutaneous administration, which results in higher anticoagulant effect without increasing bleeding tendency and ease of use without the need for blood coagulation monitoring.²

Pharmacology of LMWH differs from UFH. The main differences are the highest inhibitory activity against the Xa factor compared with thrombin (IIa), anticoagulant effect difficult monitoring (factor Xa levels), prolonged half-life, and lack of complete reversibility with protamine.⁵⁸ With subcutaneous administration, peak plasma levels are reached in approximately 3-4 hours, and the half-life of elimination, with normal renal function, is within 4-6 hours.^{73,74} However, the anti-factor Xa activity remains considerable (50%) after 10-12 hours of administration. If creatinine clearance falls below 30 mL.min⁻¹, the half-life doubles.⁷⁴ Compared to UFH, the risk of thrombocytopenia (HIT) is 10 times lower. However, they are contraindicated in HIT due to the high risk of cross-reaction, approximately 90%.⁷⁵

If thromboprophylaxis with LMWH is prescribed in two daily doses (30 mg), compared to a daily dose regimen, the risk of spinal hematoma may be increased, as the minimum levels of anti-Xa activity are higher.⁷⁶

The use of LMWH in patients undergoing neuraxial block was adopted in Europe in 1987. Dosages used were 20-40 mg in a single dose 12 hours before surgery. To prevent the occurrence of spinal hematoma, guidelines recommended insertion/removal of epidural catheter at a minimum interval of 10-12 hours after the last dose of LMWH. The subsequent dose was restarted after 8-12 hours.^{5,16} Thus, reviews involving data from millions of patients showed that the use of neuraxial block in subjects on LMWH under the European regime was safe, with report of only one case of spinal hematoma.^{77,78}

On the other hand, in the United States, enoxaparin introduced in 1993 had no recommendation regarding time between drug administration and neuraxial block or catheter removal. Enoxaparin was routinely administered in the immediate postoperative period at a dose of 30 mg twice daily. After five years of use, the Food and Drug Administration (FDA) accumulated reports of 43 patients undergoing neuraxial blocks who developed spinal hematoma.⁷⁹ In 1998, 13 cases of spinal hematoma associated with LMWH had been reported in Europe, while in United States, it reached 60 cases.²⁴ Reasons for the high rates were attributed to: (i) higher daily dose prescription of LMWH; (ii) more frequent doses, possibly leading to higher minimum blood level during catheter insertion/removal; (iii) lack of practical guidelines

for neuraxial block and LMWH administration; (iv) lack of larger series.^{19,24}

After the Second American Society of Regional Anesthesia (ASRA) resolution in 2003, studies in the English literature reported 10 cases related to the combination of LMWH and spinal hematoma. Five additional cases were reported by the Royal College of Anesthetists Consensus in the UK in 97,925 epidural blocks, but without proven evidence of association with anticoagulant drugs.¹²

Recommendations

1. Antiplatelet drugs and oral anticoagulants concomitantly administered with LMWH increase the risk of spinal hematoma, and in such conditions blockade is contraindicated. In patients on ASA, it seems prudent to administer the thromboprophylactic dose of heparin postoperatively (B).³⁶ In these patients, if LMWH is administered preoperatively, wait 24 hours to perform blockade or catheter removal due to increased risk of bleeding (C);⁶
2. Bleeding during needle or catheter insertion does not justify surgery cancellation. The beginning of therapy with LMWH in this circumstance should occur 24 hours after the end of surgery (D);⁶
3. In preoperative patients receiving LMWH thromboprophylaxis, neuraxial block is recommended 10-12 hours after the last dose of LMWH (D);⁶
4. In patients on therapeutic doses of LMWH, such as enoxaparin 1 mg.kg⁻¹ every 12 hours, enoxaparin 1.5 mg.kg⁻¹ per day, dalteparin 120 IU.kg⁻¹ every 12 hours, dalteparin 200 IU.kg⁻¹ per day or tinzaparin 175 IU.kg⁻¹ per day, an interval of at least 24 hours is recommended between the last dose and neuraxial block to ensure normal hemostasis (D);⁶
5. Patients under prophylactic regimen of LMWH every 12 hours (enoxaparin 30 mg twice daily), one dose should be omitted to enable a 24 hours interval before neuraxial block or catheter removal (A);³
6. Regarding LMWH postoperative use, the first dose should be administered 6-8 hours after surgery. A second dose of LMWH should not be administered before 24 hours of the first dose. Thus, epidural catheter may be safely maintained. However, epidural catheter removal should only be done after 10-12 hours of the last dose. The subsequent dose of LMWH after catheter removal should be administered after 2 hours. No drugs that alter hemostasis should be given due to the risk of additive effects (D);⁶
7. In patients under twice daily dosage regimen, there is greater risk of spinal hematoma, and continued monitoring is recommended. The first dose of LMWH should be administered 24 hours after the end of surgery, regardless of the anesthetic technique, and only in the presence of adequate surgical hemostasis. Epidural catheter should be removed before restarting LMWH regimen. If the technique of continuous analgesia is chosen, catheter may be maintained until the morning of the day following surgery, provided that removed before the first dose of LMWH, which may be administered 2 hours after catheter removal (D).⁶

Vitamin K antagonists (coumarins)

Vitamin K antagonists include acenocoumarol, phenprocoumon, and warfarins. These drugs inhibit the gamma-carboxylation synthesis of vitamin K-dependent factors (II, VII, IX, X) and C and S proteins, which makes them unable to bind phospholipid in platelet membranes during coagulation. Prothrombin time (PT) and international normalized ratio (INR) are tests commonly used to monitor these drugs and reflect the plasma activity of three (II, VII, and X) of the four clotting factors. Clinical experiences suggest that the 40% activity level of each factor is adequate for normal hemostasis, or near normal.⁸⁰ INR of 1.5 is associated with the 40% activity of factor VII.⁸¹ Because factor VII has a shorter half-life (about 6 hours), the initial increase of INR when coumarin anticoagulants are used reflects the loss of factor VII activity. However, these drugs therapeutic effect is more dependent on the reduction of factors II and X, which have half-lives relatively longer, 60 to 72 hours and 24 to 36 hours, respectively. After warfarin discontinuation, factor II is the latest to normalize.⁸² Thus, after drug discontinuation, INR may return to near normal values due to the activity restoration of factor VII. However, factors II and X may not have been restored to normal hemostatic levels.⁸¹ Its anticoagulant effect can be effectively prevented by vitamin K, fresh frozen plasma or prothrombin complex concentrate (II, VII, IX, and X factors) administration.²

Although the ASRA has recommended epidural catheter removal with INR less than 1.5, this value has been considered as conservative. Reports show epidural catheter removal with INR higher and uneventful.^{83,84} If it occurs in the first 48 hours of medication use, it is likely that there are adequate levels of clotting factors activity, particularly II and X factors. Beyond this period, all vitamin K-dependent clotting factors will be affected. There was no reported case of spinal hematoma in 11,235 patients receiving epidural analgesia after total knee arthroplasty, and treated with warfarin (5-10 mg) started the night before the procedure. Epidural catheters were removed 48 hours postoperatively. Mean INR at recession time of was 1.5 (0.9-4.3). INR was less than 1.5 in approximately 40% of cases. These series suggest that not only the INR value should be considered during epidural catheter management, but also the duration of therapy with warfarin, and that a prolonged time for more than 48 hours may represent significant increased risk of hematoma.⁸⁴

Perioperative management of patients on warfarin remains controversial. Recommendations are based on drug pharmacology, clinically relevant levels, and deficiency of vitamin K-dependent clotting factors, case series, and spinal hematoma reports.⁶

Recommendations

1. Neuraxial blockade should only be performed 4-5 days after drug discontinuation, confirmed by normal INR. Consider that in the first three days after drug discontinuation, coagulation (reflected primarily by levels of factors II and X) may not be adequate for hemostasis, despite a decrease in INR (indicating a return of factor

VII activity). Appropriate levels of factors II, VII, IX, and X may not be present until INR is within the reference range (B);⁶

2. If warfarin thromboprophylaxis was initiated postoperatively, remove neuraxial catheter with an INR less than 1.5. This value was obtained from studies that correlated hemostasis with clotting factor activity levels greater than 40%. In these, neurological monitoring must be kept for least 24 hours after catheter removal (D);⁶
3. When replacing coumarin by LMWH or UFH preoperatively, consider the UFH and LMWH recommendations for neuraxial block (D);²
4. If patient is on low doses of warfarin during epidural analgesia, INR monitoring should be done daily (D).⁶

Factor Xa inhibitors

Fondaparinux (Arixtra®)

Fondaparinux is a synthetic selective pentasaccharide that indirectly inhibits factor Xa. Unlike the LMWH, it has no effect on factor IIa (thrombin). Platelet aggregation is unaffected.³ This compound has approximately 100% bioavailability after subcutaneous administration and half-life of elimination of 18-21 hours, primarily by the kidneys. Half-life is prolonged to 36-42 hours when creatinine clearance is less than 50 mL.min⁻¹, and is contraindicated in patients with clearance less than 30 mL.min⁻¹.⁸⁵ Prophylactic dose is 2.5 mg via subcutaneous route once daily.

Fondaparinux is usually administered 6-12 hours after surgery, as its preoperative use may increase the risk of surgical bleeding without improving antithrombotic efficacy.⁸⁶ Because it is used postoperatively, there are no problems with single puncture neuraxial anesthesia. However, if the catheter is inserted, it should be removed only in the absence of fondaparinux plasma levels. The recommendations for epidural catheter management in patients on fondaparinux are based on the conditions used in the study by Singelyn et al.⁸⁷ This study evaluated 5,387 patients, of whom 1,428 underwent regional anesthesia, and the single dose of fondaparinux the night before catheter removal was omitted. Thus, the research team ensured an interval of 36 hours between the last dose and catheter removal and 12 hours between catheter removal and the subsequent dose of fondaparinux. There was no case of spinal hematoma and no increased risk of DVT.⁸⁷

According to the American College of Chest Physicians (ACCP), even with two reported cases of HIT with fondaparinux, its use in patients with a history of HIT is suggested as an option to UFH or LMWH.⁸⁸

Recommendations

1. At prophylactic dose (2.5 mg) fondaparinux may be used in postoperative with atraumatic neuraxial anesthesia. If used, epidural catheter should be removed only after 36 hours of the last dose and the subsequent dose administered only after 12 hours of removal (D);³
2. Neuraxial anesthesia is contraindicated when fondaparinux (5-10 mg.day⁻¹) is used in therapeutic doses due

to the risk of unpredictable residual effect in the body (D).³

Rivaroxaban (Xarelto®)

Rivaroxaban is a selective inhibitor of factor Xa. It is orally administered and approved for DVT prevention after total knee and hip replacement surgery. Treatment is initiated 6-8 hours after surgery; with a single dose of 10 mg, peak plasma levels are achieved in 2-4 hours. Studies show better efficacy compared to enoxaparin for thromboprophylaxis,⁸⁹ as well as compared to heparins and vitamin K antagonists for treating DVT.⁹⁰

Rivaroxaban has a half-life of 5-9 hours, is poorly influenced by renal function (33% clearance occurs via kidneys), as it also has hepatic clearance. However, in the elderly, the half-life may be prolonged to 11-13 hours.³

Rivaroxaban prolongs aPTT and HepTest, but these tests are not recommended to evaluate the drug anticoagulant effect.⁹¹ Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent manner, with close correlation with plasma concentrations,⁹² and should be measured in seconds and not by INR. However, routine monitoring is not considered necessary. Similar to most new anticoagulants, rivaroxaban cannot be antagonized.²

Recommendations

1. Due to the lack of prospective studies, an interval greater than two half-lives of elimination is recommended (24 hours) to perform neuraxial block or epidural catheter removal;²⁸
2. Because peak plasma level occurs within 2-4 hours, the subsequent dose should be given 4-6 hours after catheter removal (D);²⁸
3. If there is traumatic puncture with bleeding, rivaroxaban should be delayed for 24 hours (D).⁹¹

Apixaban (Eliquis®)

Apixaban is a direct factor Xa inhibitor, administered orally. It has 60% bioavailability and does not require biotransformation for activation.⁹³ In contrast with vitamin K antagonists, apixaban does not interact with food. Peak plasma levels are reached in 3 hours, half-life is about 12 hours (10-15 hours), and two daily doses are required.^{93,94} There is no need for routine coagulation monitoring. Kidneys eliminate only 25% and the hepatic and biliary metabolisms eliminate 75%, excreted via the bowel.

Randomized studies have shown the efficacy and safety of apixaban after knee and hip replacement surgeries.⁹⁵⁻⁹⁷ Evaluation of 18,201 individuals with atrial fibrillation, which compared apixaban with warfarin, showed that apixaban was superior in thromboprophylaxis, with low risk of bleeding and lower mortality rate.⁹⁸ Based on these studies, apixaban is likely to be approved for anticoagulation in non-valvular atrial fibrillation and thromboprophylaxis in hip and knee surgeries.

Recommendations

1. Use the same rules for new anticoagulants; i.e., interval of two half-lives of elimination (20-30 hours) to perform neuraxial block or remove epidural catheter (D);³
2. After catheter removal, restart apixaban within 4-6 hours (D).³

Thrombin inhibitors

Dabigatran (Pradaxa®)

Dabigatran is a new thrombin reversible inhibitor orally administered and recently approved for DVT prophylaxis in patients undergoing hip or knee replacement surgery.⁹⁹ Dabigatran is administered as the prodrug (dabigatran etexilate), which is converted to dabigatran by plasma esterases. This compound has a half-life of 12-17 hours, eliminated mainly by the kidney, and cannot be antagonized. After administration, peak plasma levels are reached in 2-4 hours. Effects of continuous use may persist for 5-7 days, depending on renal function.¹

Treatment is initiated 1-4 hours after surgery at doses ranging from 75 mg (creatinine clearance 30-50 mL.min⁻¹) to 110 mg (normal renal function). Dosage is escalated to 150 mg to 220 mg on subsequent days. Dabigatran prolongs aPTT without linear effect. Thrombin time (TT) is particularly sensitive and reference for anticoagulation management, with linearity between dose-response in therapeutic concentrations.¹ Anticoagulation reversal is theoretically possible by administration of recombinant factor VIIa, although not clinically tested.¹⁰⁰

The effectiveness of dabigatran (220 mg) for DVT prevention is compared to that of enoxaparin (40 mg.day⁻¹) and without increased bleeding.¹⁰¹ Preliminary studies of dabigatran and neuraxial block were conducted with epidural catheter removal 4-6 hours before the first dose. There is no study of patients on dabigatran and use of epidural catheters.

Recommendations

1. Because DVT prophylaxis with dabigatran is initiated postoperatively, there is no limitation to simple neuraxial block (D);³
2. Dabigatran discontinuation should be at least seven days before neuraxial block to allow return to normal coagulation (D);¹
3. The half-life of 12-17 hours suggests a 34 hours interval between the last dose and catheter management or removal. However, the manufacturer's¹⁰² recommendation is to *avoid* epidural catheter in patients on this drug and that the first dose should be administered at least 2 hours after catheter removal (D);³
4. However, because plasma level can be reached in 2 hours, it is prudent to observe a minimum interval of 6 hours after catheter removal to start drug administration (D).²

Argatroban (Argatra®)

Argatroban is a direct thrombin reversible inhibitor that binds to the different forms of thrombin.^{103,104} It is indicated for patients with thrombosis associated with heparin-induced thrombocytopenia (HIT) by the lack of interaction with platelet factor 4 (PF4).²

Argatroban is administered by continuous IV infusion and eliminated exclusively by the liver, and may be used in renal failure. The dose of 0.5-2 µg.kg.min⁻¹ is adjusted to maintain aPTT within 1.5 to 3 of the normal value. In patients with good liver function, aPTT normalization occurs 2-4 hours from the end of infusion due to the short half-life of 35-45 minutes.¹⁰⁵

Recommendations

1. The insertion of spinal/epidural needle/catheter should be made at least 4 hours after drug discontinuation. The drug reintroduction time after the blockade or catheter removal is 2 hours and always excluded residual coagulant effect by aPTT and ACT measurements (D);²
2. If the patient is under argatroban therapy due to diagnosis of acute HIT, treatment should not be discontinued because of the risk of thromboembolism and, therefore, blockade is contraindicated (D).²

Desirudin (Iprivask®) e lepirudin (Refludan®)

Recombinant hirudins (lepirudin and desirudin) are from the first generation of direct thrombin inhibitors and are parenterally administered. They have no interaction with platelet factor 4 (PF4) and, therefore, do not trigger heparin-induced thrombocytopenia (HIT). Desirudin is indicated for DVT prophylaxis and lepirudin for DVT treatment of patients with history of HIT.³

Both lepirudin and desirudin have half-lives of 1.3-2 hours, but it increases significantly in renal failure. Due to the potential risk of bleeding, the anticoagulant effect of hirudin should be routinely monitored with aPTT or ecarin clotting time (ECT).¹⁰⁶

Recommendations

1. In patients with normal renal function, wait 8-10 hours from last dose to perform neuraxial block with or without epidural catheter installation (D);³
2. In patients with normal renal function, wait 8-10 hours from last dose to remove catheter (A);³
3. Wait 2-4 hours to restart these drugs after puncture or epidural catheter removal (D);³
4. Absence of residual anticoagulant effect should always be confirmed by determining aPTT and ECT (D).³

Neuraxial block and laboratory tests

Current guidelines and consensus state that neuraxial block should not be performed in patients with thrombocytopenia; however, none of them determine the minimum limit of platelets number to perform neuraxial block.⁴

Platelet function appears to be more important than the isolated number of, platelet.¹⁰⁷ Researchers suggest a platelet count greater than 50,000.mm⁻³ with preserved function as acceptable, while a platelet count greater than 100,000.mm⁻³ is acceptable without considering evaluation test of platelet function.^{108,109}

A recent study reported that in the absence of risk factors, platelet count > 80,000.mm⁻³ is considered safe to perform spinal/epidural blocks and platelet count > 40,000.mm⁻³ to perform simple lumbar puncture.¹¹⁰

Regarding secondary hemostasis, the 40% activity level of each factor is adequate or near normal for normal hemostasis.⁸⁰ INR of 1.5 is associated with the 40% activity of factor VII. Bleeding may occur if the level of any coagulation factor is reduced to 20-40% of its normal value.⁸¹

Recommendations

1. Epidural or spinal blocks, in the absence of risk factors for bleeding, may be performed with platelet count above 80,000.mm⁻³ (D);¹¹⁰
2. INR <1.5 is considered safe to perform neuraxial blocks (D).⁶

Peripheral nerve blocks and anticoagulants

Although spinal hematoma is the most important hemorrhagic complication of regional anesthesia because of the catastrophic nature of bleeding into a restricted and non-compressible space, the associated risk after plexus and peripheral nerve blocks remains undefined.

The presence of hematoma may increase morbidity and mortality, and there are reported cases involving retroperitoneal hematoma after lumbar plexus block with the use of enoxaparin or clopidogrel. In one of these reports, the catheter inserted into the lumbar plexus was removed 1.5 hours after the last dose of heparin.^{111,112}

Although most of the cases have evolved without neurological damage, there was extension of the hospital stay, with injury and patient dissatisfaction, as well as need for transfusion of packed red blood cells. Some showed deficits engines and sensitives, renal failure and death by bleeding.¹¹¹⁻¹¹³

The German Society of Anesthesiology and Intensive Care Medicine adopts the same recommendations for neuraxial, peripheral nerve, and plexus blocks in patients on antithrombotic drugs.¹¹⁴ The Austrian Society differentiates neuraxial blocks from deep or superficial peripheral blocks.¹¹⁵ These latter, similar to axillary brachial plexus, femoral nerve, and distal sciatic blocks, may be performed with the use of ASA and anticoagulants.¹¹⁵

With the increasing use of ultrasound to aid peripheral nerve and plexus blocks, the number of complications, such as vascular puncture, decreased because of the dynamic visualization of structures adjacent to the nerve to be blocked.¹¹⁶ Thus, evidence probably will demonstrate the actual decrease in complication rates with this technique and, therefore, recommend the relatively safe use of peripheral nerve blocks guided by ultrasound in anticoagulated patients.

Recommendations

1. Respect the interval between LMWH administration and insertion/removal of catheters similar to those used for neuraxial blocks (D);³
2. Do not remove any catheter in the period of anticoagulant greatest activity (D);³
3. Because morbidity is associated with retroperitoneal hematoma, paravertebral or lumbar plexus blocks have the same recommendations used in neuraxial blocks (D).¹¹¹
4. Superficial blocks, such as axillary, femoral or distal sciatic, may be performed with the use of anticoagulation or antiplatelet therapy (D).¹¹¹

Conflicts of interest

The authors declare no conflicts of interest.

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