Current Pain and Headache Reports (2019) 23: 67
https://doi.org/10.1007/s11916-019-0805-x

OTHER PAIN (A KAYE AND N VADIVELU, SECTION EDITORS)

Regional Anesthesia in Patients on Anticoagulation Therapies—Evidence-Based Recommendations

Alan David Kaye[1] · Andrew J. Brunk[2] · Aaron J. Kaye[3,4] · Jordan S. Renschler[5] · Brendon M. Hart[6] · Prathima Anandi[7] · Shilpa Patil[6] · Elyse M. Cornett[6] · Charles J. Fox[6]

Published online: 29 July 2019

Abstract

Purpose of Review Anticoagulant use among patients is prevalent and increasing. It is important for anesthesiologists to be aware of patients on anticoagulants while performing regional anesthesia.

Recent Findings In recent years, the FDA has approved many new anticoagulants. With new drugs coming to the market, new side effect profiles should be considered when treating patients, especially when using regional anesthesia. Both ASRA and European agencies have laid out recommendations regarding anticoagulant use and neuraxial/regional techniques. Regarding newer anticoagulants, the guidelines for discontinuation prior to neuraxial injection are based on pharmacokinetics, including half-life duration for each drug.

Summary While each clinical scenario requires an individualized approach, general guidelines can serve as a starting point to help with anesthetic planning and potentially improve patient safety in this evolving field.

Keywords Regional anesthesia · Anticoagulation therapies · Neuraxial anesthesia · Evidenced-based practice · Anticoagulants

Introduction

Administration of regional anesthesia for patients on anticoagulant therapies is an important, evolving practice. As the number of patients on anticoagulant treatments increases, and the popularity of regional anesthesia continues to rise, it is critical for clinicians to be aware of the associated risks and proper management.

This article is part of the Topical Collection on *Other Pain*

✉ Elyse M. Cornett
ecorne@lsuhsc.edu

Alan David Kaye
akaye@lsuhsc.edu

Andrew J. Brunk
abrunk@lsuhsc.edu

Aaron J. Kaye
aaronkaye44@yahoo.com

Jordan S. Renschler
jrensc@lsuhsc.edu

Brendon M. Hart
bhart1@lsuhsc.edu

Prathima Anandi
Prathima.anandi@VUMC.org

Shilpa Patil
spati1@lsuhsc.edu

Charles J. Fox
cfox1@lsuhsc.edu

[1] Department of Anesthesiology, LSU Health Sciences Center, Room 656, 1542 Tulane Ave., New Orleans, LA 70112, USA

[2] Department of Anesthesiology, LSU Health New Orleans, 1542 Tulane Ave, New Orleans, LA 70112, USA

[3] Medical University of South Carolina, Charleston, SC 29425, USA

[4] Department of Anesthesiology, LSU Health Sciences Center, Room 656, 1542 Tulane Ave., New Orleans, LA 701123, USA

[5] Department of Anesthesiology, LSU Health Sciences Center, 1901 Perdido St., New Orleans, LA 70112, USA

[6] Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport, LA 71103, USA

[7] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

There are several risks associated with regional anesthesia. One example is spinal epidural hematoma, a potentially catastrophic complication of neuraxial anesthesia. The overall incidence is low, reportedly ranging from 1 in 18,000 to 1 in 150,000 with epidural anesthesia and 1 in 158,000 to 1 in 220,000 with spinal anesthetics [1, 2]. However, a number of factors can increase the risk. Advanced age, female gender, underlying inherited coagulopathy, thrombocytopenia, and spinal disorders have been associated with hematoma during neuraxial blockade [3•]. Additionally, difficulty performing neuraxial blockade and placement of an indwelling epidural catheter augment bleeding risk [4••].

Drug-induced coagulopathy is another risk factor for hematoma after regional anesthesia. While the majority of research has focused on neuraxial anesthesia, the research involving peripheral regional anesthesia is less robust. As such, the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends that clinicians manage anticoagulation for patients undergoing perineuraxial, deep plexus, or deep peripheral blocks similar to those of patients undergoing neuraxial blockade. ASRA recommends using block site compressibility, vascularity, and ramifications of hemorrhage to help guide management of other peripheral blockades [4••]. Anticoagulant management is agent-specific, as each anticoagulant has a unique pharmacological profile. The majority of anticoagulants carry a black box warning for increased risk of spinal hematoma. Practitioners must have an understanding of the risk associated with each agent, as it can vary even for drugs within the same general category. Whereas platelet P2Y12 receptor blockers and platelet GPIIb/IIIa receptor antagonists carry significant risk, monotherapy with non-steroidal anti-inflammatory drugs has not shown increased risk of hematoma [5]. In this regard, concomitant use of herbal and over-the-counter products can result in additive or synergistic effects contributing to increased bleeding risk.

For agents known to increase the risk of hematoma, the time to peak effect and elimination half-time guide optimal timing of regional anesthesia. Unfortunately, patients do not all respond to antithrombotic medications in the same manner. For example, impaired renal function delays enoxaparin clearance [6]. Furthermore, variability in renal function for a single patient over time alters anticoagulant elimination. Anesthesia providers must interpret each patient's response to anticoagulation in the context of factors that independently increase the risk of hemorrhage, such as those listed in Table 1. A broad medical knowledge base is also necessary for good management. There are numerous indications for antithrombotic and antiplatelet treatment. Practitioners must understand the underlying conditions warranting these treatments to assess risk-benefit profile of altering treatment regimens to optimize anesthetic management.

Table 1 Factors increasing risk of significant hemorrhage with regional anesthesia [3•, 4••]

Inherited or acquired coagulopathy	Thrombocytopenia
Dual antiplatelet or anticoagulant therapies	Advanced age
Spinal or vertebral column abnormalities	Female gender
Difficulty of needle placement	Placement of a catheter

While each clinical scenario requires an individualized approach, general guidelines can serve as a starting point to help with an anesthetic planning. In this article, we discuss antithrombotic guidelines for patients with planned regional anesthetics and review numerous anticoagulant and antiplatelet agents.

Guidelines for Antithrombotic Therapy

There has been a shift in anticoagulation treatment over the past few years with the FDA approval of newer anticoagulants. With new drugs coming on the market, new side effect profiles must also be considered. Neuraxial techniques have long been used in multiple surgical modalities to allow for anesthesia and analgesia. It is important to delineate the new recommendations for these new anticoagulants. Both ASRA and European agencies have laid out recommendations regarding anticoagulant use and neuraxial/regional techniques.

Regarding new anticoagulants, the guidelines for discontinuation prior to neuraxial injection are based on half-life. It is generally considered that two half-lives are necessary prior to any neuraxial injection based on safety profile and preventing complications including spinal hematoma, as well as venous thromboembolism (VTE), while being off anticoagulation [7]. Guidelines for stopping the newer anticoagulants are based on studies regarding their pharmacokinetics. During this time, low molecular weight heparin can be employed since the effect of low molecular weight heparin (LMWH) is essentially gone by the time neuraxial would be performed [7]. The incidence of complications regarding insertion of neuraxial catheters is the same regarding removal of the catheters in patients who take anticoagulants.

Drugs

Oral Anticoagulants and Heparins

Patients taking oral anticoagulants are at higher risk for neuraxial and surgical procedures. Typically, any patient taking warfarin is monitored by frequent international normalized ratio (INR) and prothrombin time (PT) blood draws. Warfarin targets factors II, VII, IX, and X. Typically, the PT and INR normalizes in 3–5 days after discontinuation of warfarin. It is recommended that documentation of a normal PT and INR

within the reference range is obtained prior to neuraxial procedures. INR should be obtained daily while any neuraxial or perineural catheters are present. It is also recommended to allow the INR to be less than 1.5 prior to removal of an indwelling neuraxial catheter. If the INR is between 1.5 and 3, removal should be performed on a case-by-case basis with neurological exams postremoval [8••]. In patients receiving unfractionated heparin or who will be undergoing vascular surgery, it is important to delay heparin for 1 h after any neuraxial or epidural technique. If systemic anticoagulation needs to be achieved with an epidural in place, it is important to discontinue systemic heparin for 2–4 h before the catheter is removed and wait 1 h until restarting systemic heparin. There is no contraindication for patients receiving less than 10,000 units of subcutaneous heparin daily, although it is important to monitor the platelet count on patients who are receiving prolonged subcutaneous heparin prior to catheter removal [8••].

Enoxaparin is the most common low molecular weight heparin used in the hospital setting. In patients receiving a thromboprophylaxis dose, it is necessary to wait 10–12 h prior to neuraxial techniques. If enoxaparin is being dosed at therapeutic levels, 24 h is the necessary time frame to wait prior to neuraxial techniques. Catheters should be removed prior to initiation of twice-daily LMWH. It can be dosed 2 h after catheter removal or 24 h after needle/catheter placement, whichever one is later. Dosing should occur 6–8 h after needle/catheter placement with once-daily dosing of LMWH [8••].

Antiplatelets

Antiplatelet therapy is used as an adjunct for pain control in a variety of cases that also concurrently use neuraxial techniques. Additionally, antiplatelet therapy is also prescribed for patients who also receive anticoagulation. The concurrent use of antiplatelets and heparin or other anticoagulants increases the risk of complications and bleeding. Non-steroidal anti-inflammatory agents do not increase the risk of spinal hematoma by themselves, and there are no restrictions to their use. Ticlopidine, clopidogrel, and GPIIb/IIIa antagonists need to be considered. Wait 14 days after discontinuation of ticlopidine, 5-7 days for clopidogrel, and 7–10 days for prasugrel to allow platelet function to return. Despite the possibility of a normal platelet count, they will not be functioning appropriately. For the GPIIa/IIIb inhibitors, the range is 8 to 48 h prior to neuraxial techniques [8••].

Thrombin Inhibitors

The recombinant hirudins are first-generation direct thrombin inhibitors. They are indicated for thromboprophylaxis in those who need thromboprophylaxis or DVT treatment in patients with heparin-induced thrombocytopenia. They have an elimination half-life of 30 min to 3 h. Monitoring can be done by following partial thromboplastin time (PTT) levels. It is recommended to wait 8–10 h after discontinuation prior to any neuraxial technique, and longer in renal insufficiency. A PTT should be normalized prior to puncture. Dosing may continue 2 to 4 h after the procedure [9]. The old recommendation for patients who have received or are receiving thrombolytics was to wait 10 h after a neuraxial technique to administer thrombolytics. However, recent ASRA recommendations suggest waiting 48 h after a neuraxial technique to administer thrombolytics. Documented coagulation studies including fibrinogen are recommended prior to proceeding. If there is concurrent use of epidural and fibrinolytics, neurologic function should be assessed every 2 h [10•].

Herbal Medications

Herbal drugs including garlic, gingko, and ginseng by themselves do not appear to increase the risk of spinal or epidural hematoma in neuraxial techniques when used alone; however, many of these including garlic, gingko, and ginseng interfere with the coagulation cascade, and many of these products have been linked in case reports to bleeding including spinal or epidural hematoma. The American Society of Anesthesia has recommended that all of these products be stopped 2 to 3 weeks prior to surgery or pain procedures given the half is unknown and thus allows for elimination of these products. Data on using herbal medicines in combination with other anticoagulants is lacking, but it is certain to assume that the bleeding risk is additive or synergistic when combined with other anticoagulants [8••]. There are no accepted tests to monitor herbal medication use, and there are no recommendations regarding timing and removal of catheters in relation to prior dose of herbal medications [11•].

New Oral Anticoagulants

Balancing the use of anticoagulants to reduce thromboembolic events and the risk of perioperative bleeding associated with the anticoagulants is crucial [3•, 9]. Several new oral anticoagulants have been approved in recent years; however, there are limited clinical evidence-based recommendations available on managing these anticoagulants when administering regional anesthesia [12]. ASRA guidelines are pharmacologically driven when evidence is unavailable for new therapies [12]. To optimize patient safety and prevent life-threatening events perioperatively, physicians must consider the pharmacodynamics of anticoagulation therapy.

Appropriate timing of withdrawal of anticoagulants is dependent on half-life ($T_{1/2}$), which may be altered by patient characteristics [3•]. For example, patients who are elderly or

have renal impairment may have extended $T_{1/2}$, requiring longer preoperative discontinuation of the anticoagulants for sufficient clearance [3•]. European guidelines recommend that neuraxial and deep peripheral nerve blocks should not be performed until at least 2–$T_{1/2}$ after discontinuation of the anticoagulative therapy [13]. More conservative recommendations suggest that in high-risk patients and patients using new anticoagulants with limited clinical experience, the anticoagulants should be withdrawn 5–$T_{1/2}$ before surgery [12]. In this regard, Benzon and colleagues, in 2013, suggested that discontinuing the use of the anticoagulants for an interval of five half-lives of the drug and using a low molecular weight heparin (LMWH) for bridging therapy in patients with high risk of venous thromboembolism (VTE) are a compromise between conservative recommendations and the European guidelines.

Apixaban

Apixaban is an anticoagulant approved to prevent stroke in patients with non-valvular atrial fibrillation [12]. Apixaban is also indicated for VTE prophylaxis after total joint surgery [12]. Apixaban at 5 mg per day was found to reduce the risk of VTE, with less risk of major bleeding than warfarin [7]. It is a reversible factor Xa inhibitor with a $T_{1/2}$ of 13–15 h. Apixaban is administered orally and is removed via renal (25%) and intestinal excretion (75%) [9, 12]. Inhibitors of CYP3A4 decrease metabolism of apixaban; therefore, it is not recommended with potent CYP3A4 inhibitors such as azoles and ritonavir, an HIV protease inhibitor [3•, 7]. The European Society of Anaesthesiology (ESA) suggests that performing neuraxial blockade in patients using apixaban should be done with extreme caution [13]. The ASRA currently recommends halting apixaban use 5–$T_{1/2}$, or 75 h, before pain procedures. Resumption of therapy may begin as soon as 24 h after the procedure, as with most of the new anticoagulants [12].

Dabigatran

Dabigatran is a direct thrombin inhibitor that functions to block thrombin from interacting with its substrates, thus preventing clot formation. It is used for thromboprophylaxis following major hip or knee surgery [3•]. Dabigatran is given orally (220 mg loading dose then 110 mg once daily) as a prodrug and is activated in the stomach [12]. The $T_{1/2}$ of dabigatran is around 14 h, and it is primarily cleared by the kidney (80%) [3•, 12]. Due to the heavy reliance on the kidney for clearance of dabigatran, dosing must be reduced for patients with renal impairment [3•]. The ASRA, ESRA, and World Institute of Pain currently recommend 5–$T_{1/2}$, or 4–5 days, between the last dose and performing regional anesthesia [12]. Like most of the anticoagulants, dabigatran may be resumed 24 h after the procedure. Shorter times may be considered for preprocedural discontinuation and postprocedural recontinuation at the discretion of physicians [12].

Fondaparinux

Fondaparinux inhibits factor Xa indirectly and is also used for VTE prophylaxis after major joint surgery [12]. The American College of Clinical Pharmacy (ACCP) currently recommends fondaparinux to prevent thrombosis in patients with a history of heparin-induced thrombocytopenia (HIT) [13]. The current recommended dose is 2.5 mg at least 6–8 h postoperatively [13]. Fondaparinux has a relatively longer $T_{1/2}$ of 18 h and is primarily cleared by renal excretion. Because it is given postoperatively, the main consideration of fondaparinux surrounds catheter removal. The EXPERT study concluded that discontinuing fondaparinux for 48 h before catheter removal facilitated the safety of neuraxial blockade without increasing the risk of VTE [14].

Rivaroxaban

Rivaroxaban is a factor Xa inhibitor approved for the prevention of stroke, non-valvular atrial fibrillation, and thromboprophylaxis [12]. It is given at varying doses 6–8 h postoperatively, then once daily [9]. Rivaroxaban has a shorter $T_{1/2}$ of 5–9 h and is cleared by the gut, liver, and kidney equally [12]. It is contraindicated in patients with liver disease, and dosing must be adjusted for those with renal insufficiency [9]. There is little clinical data surrounding regional anesthesia utilization and rivaroxaban; therefore, the ASRA, ESRA, and World Institute of Pain recommend waiting 5–$T_{1/2}$ between withdrawal and regional anesthetic; however, recommendations are also dose-dependent [9]. According to the ASRA, for patients taking less than 10 mg daily, 2–$T_{1/2}$ may be sufficient prior to neuraxial injection. For patients taking more than 10 mg daily, the ASRA recommends waiting 5–$T_{1/2}$ to allow for sufficient clearance. It is recommended to wait 6 h before resuming rivaroxaban after injection or removal of catheter [12].

Danaparoid

Danaparoid was used for VTE prophylaxis and treatment in patients with a history of HIT type II; however, it was removed from the market in the USA in 2002 [13, 15]. It works primarily by antithrombin-mediated inhibition of factor Xa and has a long $T_{1/2}$ of 22 h [9]. This $T_{1/2}$ is prolonged in patients with renal insufficiency, and there is no antidote available [13]. Cases of severe bleeding have been associated with danaparoid, and it has no antidote but can be removed by

plasmapheresis [9, 13]. Danaparoid should only be given post-operatively and should be avoided with use of catheters [13].

Idrabiotaparinux

Idrabiotaparinux is a factor Xa inhibitor. It was reformulated from idraparinux, which failed to pass clinical trials due to the major bleeding it caused [9]. Because of idrabiotaparinux's long $T_{1/2}$ (135 h) and reliance on the kidneys for excretion, it is only given via subcutaneous injection once weekly and should be given to the elderly and those with renal insufficiency with extreme caution [9]. Avidin is an available antidote in cases of accumulation of idrabiotaparinux [13]. There is currently insufficient data on the implications of idrabiotaparinux in regional anesthesia and should therefore be avoided [9, 13].

Challenges and Solutions

One downside to regional anesthesia is the increased risk of bleeding-related complications that may occur in conjunction with direct oral anticoagulant use. Although rare, these complications must be recognized and treated promptly. Even before the procedure, prevention with medication cessation and reversal and insurance of proper coagulation function should be prioritized.

Anticoagulation Management in Central Neuraxial and Peripheral Blockade

Although there have been no cases in the literature of subdural or epidural hematomas reported with the use of dabigatran, etexilate, or rivaroxaban during central neuraxial blockade (CNB), it is important to follow a standardized approach to management of anticoagulated patients when performing CNB. The following table adapted from Green and Machin summarizes this approach (see Table 2) [16].

Management of Subdural and Epidural Hematomas (SHE)

The most feared bleeding complications of CNB are subdural and epidural hematomas. The overall incidence is exceedingly rare with estimates between 1 in 220,000 and 1 in 320,000 [17]. However when heparinized, the incidence increases to 1 in 2900 [17]. With ASA therapy, the risk is between 1 in 8500 and 1 in 12,000 [18]. In these patients, external injury (catheter insertion or spinal puncture) of a vascular structure leads to the formation of a hematoma, in the epidural or subdural space. The expansion of the hematoma can lead to pressure on the spinal cord or cauda equina. Sequelae of the condition include progressing motor and sensory blockade, bowel and bladder dysfunction, and back pain [19].

Table 2 Standard approach to manage patients on anticoagulants when performing CNB

Recommendation	Comments
1. Personalized assessment for the risks of venous and arterial thrombosis versus the benefit of CNB	Strongest indications for continuing anticoagulation: Recent VTE, clopidogrel cessation within a month of coronary stent placement, Afib with increasing CHADS-2 scores
2. Personalized assessment for risk of bleeding	Bleeding history, clinical examination, drug history, and laboratory values
3. Avoid procedures in people on multiple anticoagulant/antiplatelet therapies	Additive or synergistic effect
4. Ensure normal hemostasis before catheter insertion and removal	Minimum platelets 50 to 100 × 10^9/L INR < 1.5
5. Follow the previously mentioned guidelines for cessation and initiation intervals of specific anticoagulants prior to and after catheter insertion and removal	Dabigatran: 5–$T_{1/2}$, or 4–5 days, between the last dose and performing regional anesthesia Fondaparinux: discontinue for 48 h before catheter removal Rivaroxaban: 2–$T_{1/2}$–5–$T_{1/2}$ cessation, 6 h before resuming after injection or removal of catheter
6. Utilize close neurological monitoring after catheter insertion and removal to monitor for compressive hematomas	Neurological observation should be performed every 4 h and continue for at least 24 h after catheter removal

Management involves obtaining a stat MRI or CT scan, anticoagulant reversal if available, and obtaining an emergency neurosurgical consult. Delays can directly affect morbidity and even mortality. If indicated, laminectomy and timely evacuation of the hematoma are essential to prevent permanent loss of neurologic function [20].

Though our medical literature indicates that for many anticoagulant agents, significant complications such as spinal hematoma are rare, it should be appreciated that many anticoagulant-mediated or anticoagulant-modulated complications, including spinal and epidural hematomas, end up in ligation and are not documented in publications on this very important topic. Therefore, it behooves the clinical anesthesiologist to minimize risk and put systems in place to assess and to direct the patient to stop any medications that can potentially result in morbidity or mortality. Even in the highest risk patients who can potentially have devastating complications when off their anticoagulant therapies, the clinician should establish best practice strategies to reduce risk. For example, policies should be in place for any patient on an herbal product known to possess anticoagulant properties, or fish oil, or a serotonin-modulating antidepressant with anticoagulant effects, or a non-steroidal agent, or aspirin to reduce the likelihood of a potential clinically relevant bleeding event.

Conclusions/Summary

Regional anesthesia is a highly prevalent tool for providing analgesia in a variety of healthcare settings. These techniques avoid many of the risks and pitfalls assoacited with general anesthesia and systemic analgesia, such as venous thromboembolism induced by immobilization, and respiratory depression. Regional anesthesia also has the added benefit of sparing opioid requirements intraoperative and postoperative [21]. As such, regional anesthesia for patients on anticoagulant therapies is an evolving practice, and it is critical for clinicians to be aware of the associated risks and proper management of patients taking these medications. Healthcare providers should prioritize individualized patient care in this population, as patients do not all respond to antithrombotic medications in the same manner. The appreciation of different targets of these many agents in the coagulation cascade is clinically relevant with multiple agents in combination potentially resulting in additive or synergistic bleeding risks. The general guidelines and clinical best practice strategies discussed in this manuscript can serve as a starting point to help with individualized anesthetic planning, yielding the best outcomes for patients.

Compliance with Ethical Standards

Conflict of Interest Andrew J. Brunk, Aaron J. Kaye, Jordan S Renschler, Brendon M. Hart, Prathima Anandi, Shilpa Patil, Elyse M. Cornett, and Charles J. Fox declare no conflict of interest. Alan D. Kaye discloses that he is on the Speakers Bureau for Depomed, Inc. and Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Tryba M, Dietrich G. Epidural regional anesthesia and low molecular heparin: pro. AINS - Anästhesiologie Intensivmed Notfallmedizin Schmerztherapie, vol. 28. Stuttgart: © Georg Thieme Verlag; 1993. p. 179–84.
2. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology. 2004;101:950–9 [cited 2016 Dec 14]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15448529.
3.• Cappelleri G, Fanelli A. Use of direct oral anticoagulants with regional anesthesia in orthopedic patients. J Clin Anesth. 2016;32:224–35. **This recently published manuscript discusses important information regarding the use of oral anticoagulatns in pediatric patients**.
4.•• Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43:263–309. https://doi.org/10.1097/AAP.0000000000000763. **These recently published guidelines are a good reference for health care providers**.
5. Urmey WF, Rowlingson J. Do antiplatelet agents contribute to the development of perioperative spinal hematoma? Reg Anesth Pain Med. 1998;23:146–51.
6. Shaikh SA, Regal RE. Dosing of enoxaparin in renal impairment. P T. 2017;42:245–9.
7. Benzon HT, Avram MJ, Green D, Bonow RO. New oral anticoagulants and regional anaesthesia. Br J Anaesth. 2013;111:i96–113 [cited 2017 Aug 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24335403.
8.• Horlocker TT. Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy. Br J Anaesth. 2011;107:i96–i106. **This is a good review of regional anestheisa in patients on both antithrombotic and antiplatelet therapies**.
9. Li J, Halaszynski T. Neuraxial and peripheral nerve blocks in patients taking anticoagulant or thromboprophylactic drugs: challenges and solutions. Local Reg Anesth. 2015;4:21–32. https://doi.org/10.2147/LRA.S55306.
10.• Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43:263–309. **These recently published guidelines are important for health care providers**.
11.• Horlocker TT, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain

Med. 2003;28:172–97. **This important manuscript discusses risks associated with patients on anticoagulants**.

12. Narouze S, Benzon HT, Provenzano D, Buvanendran A, De Andres J, Deer T, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (Second Edition): guidelines from the american society of regional anesthesia and pain medicine, the european society of regional anaesthesia and pain therapy, the american academy of pain medicine, the international neuromodulation society, the north american neuromodulation society, and the world institute of pain. Reg Anesth Pain Med. 2018;43:225–262. https://doi.org/10.1097/AAP.0000000000000700.
13. Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM, et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol. 2010;27:999–1015 [cited 2016 Dec 14]. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003643-201012000-00001.
14. Singelyn FJ, Verheyen CCPM, Piovella F, Van Aken HK, Rosencher N, EXPERT Study Investigators. The safety and efficacy of extended thromboprophylaxis with fondaparinux after major orthopedic surgery of the lower limb with or without a neuraxial or deep peripheral nerve catheter: the EXPERT study. Anesth Analg. 2007;105:1540–7.
15. Michelson AD. Platelets: Elsevier; 3rd ed. Alan Michelson (ed): Academic Press. 2012 p. 1398
16. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000;16:321(7275):1493.
17. Green L, Machin SJ. Managing anticoagulated patients during neuraxial anaesthesia. Br J Haematol. Wiley/Blackwell 2010;149:195–208.
18. Horlocker TT. Complications of regional anesthesia and acute pain management. Anesthesiol Clin. 2011;29:257–78. https://doi.org/10.1016/j.anclin.2011.04.006.
19. Stafford-Smith M. Impaired haemostasis and regional anaesthesia.Can J Anaesth. 1996;43:R129–41.
20. Figueroa J, DeVine JG. Spontaneous spinal epidural hematoma: literature review. J Spine Surg. 2017;3:58–63. https://doi.org/10.21037/jss.2017.02.04.
21. Lawton MT, Porter RW, Heiserman JE, Jacobowitz R, Sonntag VK, Dickman CA. Surgical management of spinal epidural hematoma: relationship between surgical timing and neurological outcome. J Neurosurg. 1995;83:1–7.