

Anticoagulation and Spine Surgery

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Abstract

Study Design: Literature review.

Objective: Preoperative management of therapeutic anticoagulation in spine surgery is critical to minimize risk of thromboembolic events yet prevent postsurgical complications. Limited research is available, and most guidelines are based on drug half-lives. We aim to clarify current guidelines and available evidence for safe practice of spine surgery in this patient population.

Methods: A literature search in PubMed was done encompassing comprehensive search terms to locate published literature on anticoagulation and spine surgery. Predefined inclusion and exclusion criteria were applied and data extraction was performed.

Results: A total of 17 articles met the final inclusion criteria. Of these, 12 articles were retrospective chart reviews, 3 were prospective observational studies, and 2 were systematic reviews. Current practice suggests holding warfarin until international normalized ratio <1.4, anti-Xa drugs for 48 to 72 hours, 12 to 24 hours for low-molecular-weight heparin, and 4 to 24 hours for heparin, before surgery. Antiplatelet agents can be stopped for 1 to 3 days prior to operation (81-500 mg) but must be stopped for 1 week for doses >1 g/d. For Plavix, 5 to 7 days of discontinuation advised to prevent complications.

Conclusions: This review provides an overview of main anticoagulation agents seen in preoperative setting for spine patients. Although data is mixed and no true randomized control trials are available, there is growing evidence suggesting the aforementioned guidelines are needed to optimize anticoagulation in setting of spine surgery. Further studies are needed to elucidate risk of complications while operating under therapeutic levels of anticoagulation for a variety of comorbid conditions.

Keywords

spine surgery and perioperative anticoagulation, antiplatelet agents, blood loss surgical, postoperative hematoma, management guidelines

Introduction

Venous and arterial thromboembolic events are a major cause of morbidity and mortality in the United States.¹ Oral anticoagulation agents are critical in prevention of stroke and myocardial infarctions. Patients with atrial fibrillation, for example, have a 5-fold increase in their risk of stroke compared with the general population, and anticoagulation agents can reduce this risk by two-thirds.² It is estimated that currently 1% to 2% of the population (6 million people) suffer from atrial fibrillation and this number is expected to reach 13 million by 2050. Proper management of anticoagulation preoperatively in spine surgery is imperative to maximize benefits and minimize risks associated with temporarily stopping these agents.

There are no reviews of therapeutic anticoagulation use in the perioperative period in spine surgery to our knowledge. The purpose of this review is to highlight the results of

prospective/retrospective studies investigating the use of the most common classes of anticoagulants (including antiplatelet agents) and their data on safety of spine surgery while taking these medications and/or timeframe required to hold them and prevent harm.

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Methods

Search Strategy

PubMed was used for the literature search using the following terms: (“spine surgery” AND “anticoagulation” AND “perioperative management”) or (“spine surgery” AND “antiplatelet” AND “perioperative management”) or (“spine surgery” AND “aspirin” AND “perioperative management” AND “blood loss surgical” AND “postoperative hematoma”). The articles were limited to written in English language and the search period ended August 1, 2018.

Inclusion and Exclusion Criteria

Articles were included if the results included spine surgery and retrospective or prospective data on perioperative management of anticoagulation as well as review papers with practice guidelines. For agents where no spine literature was obtained, orthopedic data was collected (ie, hip arthroplasties). Articles discussing neuroaxis procedures such as pain- or anesthetic-related procedures were included. Articles otherwise not specific for spine procedures were excluded unless drug data relatable to spine procedures. Review articles were only included if part of association guidelines if raw data difficult to obtain. Any article with $N < 10$ participants were excluded, as were case reports.

Data Collection

Three reviewers independently assessed the literature obtained, and these studies were stored in Endnote software. Duplicates were removed and the titles and abstracts of all articles were reviewed by all authors to verify accuracy and relevance to topic at hand.

Results

The initial search yielded 495 articles, with a large portion being case reports of complications from spine surgery performed with preoperative use of anticoagulation. After review, the list was narrowed to 47 articles and due to confounding variables, such as use of multiple blood thinning agents or thromboprophylaxis deep vein thrombosis dosing instead of therapeutic anticoagulation, the list was further narrowed to 17 articles that were reviewed and included below.

Warfarin

Warfarin (coumadin), a vitamin K antagonist, has been the most popular anticoagulation agent and is the standard of care for patients with atrial fibrillation.^{3,4} Its mechanism of action causes a depression of factors VII, IX, X and II, with degree of depression dependent on dosage administered and has a half-life of 36 to 42 hours. It is indicated for prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation, as well as prophylaxis and treatment of venous

thrombosis. Warfarin is contraindicated for patients with any condition in which hazard of hemorrhage could be greater than the potential clinical benefits. Moreover, it is contraindicated in recent traumatic surgery or surgeries involving the central nervous system.⁵ Current guidelines suggest discontinuing warfarin for 5 days before operative intervention with goal international normalized ratio of less than 1.5. Because of its major drawbacks such as interactions with other drugs, risk of hemorrhage, and necessity for continued monitoring of blood levels, newer and less cumbersome-to-manage agents have been developed.

Minimal data is available on neurosurgical procedure while on warfarin. The American Society of Regional Anesthesia (ASRA) states that performance of neuraxial anesthesia or removal of epidural catheter within 24 hours of initial warfarin intake is safe. This is evidenced by showing that levels of clotting factor VII are greater than 40% during first 12 to 16 hours after initial warfarin intake. If given and procedures scheduled 24 or more hours later, it is recommended that international normalized ratio (INR) be checked.⁶

The ASRA further states that for neuraxial procedures, INR should be 1.4 or less; however, in patients whose warfarin was stopped for 5 to 6 days, the INR should be normalized to < 1.2 . Benzon et al⁷ investigated the effect of warfarin on INR and clotting factors (II, VII, IX, X) 5 days after discontinuation of warfarin. Twenty-one patients were studied, and it was found that if $INR < 1.2$, the median clotting factor activity was $> 40\%$ and considered adequate for neuraxial procedures. Because of the small number of patients with INR of 1.3 or 1.4 ($N = 2$), the data was inconclusive to infer if this INR range is acceptable for neuraxial injections.

Anti Xa Agents

Oral direct factor Xa inhibitors (such as rivaroxaban, apixaban, and edoxaban) act at the combination point between the intrinsic and extrinsic coagulation pathways and this has led to some promising targeted therapy.⁸ Rivaroxaban binds to factor Xa and provides rapid and irreversible inhibition. Its maximal concentrations appear 2 to 4 hours after oral administration and the drug is excreted with a half-life of 7 to 11 hours. It is indicated for stroke reduction in patients with nonvalvular atrial fibrillation, treatment and reduction in the risk of recurrent deep vein thrombosis and pulmonary embolism, and prevention of venous thromboembolism.⁹ There is a warning statement regarding neuraxial anesthesia and spinal/epidural puncture in setting of factor Xa inhibitor use and risk of developing an epidural hematoma specifically; however, current manufacturer's guidelines recommend speaking with physician regarding when to stop anticoagulation.

Apixaban (Eliquis). The ASRA formulated best practice guidelines due to the paucity of large, well-designed studies regarding anticoagulation in interventional spine procedures. Most of the recommendations are based on limited data available and pharmacokinetics. Lassen et al¹⁰ in a prospective, randomized,

double-blind study assessed 5407 patients undergoing hip replacement for efficacy in thromboembolic prevention and safety profile. Included in this study were individuals with epidural catheters. No adverse events were noted when apixaban was resumed 5 hours after epidural catheter removal at a dosing regimen of 2.5 mg twice daily. In the absence of high-quality evidence, the current ARSA guidelines are to discontinue apixaban 3 days prior to moderate or high-risk procedures. This is predicated on the half-life of apixaban ranging from 11.7 to 15.2 hours where only 3% of the drug would remain after 5 half-lives.¹¹

Dabigatran (Pradaxa). Dabigatran is a prodrug metabolized by stomach esterases into a direct thrombin inhibitor. The literature regarding interventional spine procedures is largely relegated to orthopedic joint surgery. Eriksson et al¹² performed a multicenter, parallel-group, double-blind study of total hip or knee replacement surgery evaluating safety and efficacy of dabigatran compared with rivaroxaban. In the study, 73% (1403) of the patients received epidural or spinal anesthesia and dabigatran was started 2 hours after surgery. Safety assessment was performed by classifying bleeding into 3 main categories: major bleeding (≥ 20 g/L fall in hemoglobin, leading to transfusion of ≥ 2 units of packed red blood cells, fatal retroperitoneal, intracranial, intraocular, or intraspinal bleeding), clinically significant bleeding (spontaneous skin hematoma ≥ 25 cm², wound hematoma ≥ 100 cm², spontaneous rectal, vaginal, gingival bleeding, epistaxis > 5 minutes, hematuria for > 24 hours and any other bleeding event judged as clinically significant by investigator), minor bleeding (those not fulfilling the criteria aforementioned). Doses of 50 mg, 150 mg, 225 mg twice daily and 300 mg daily were compared. Major bleeding for these dosages were as follows N = 1 (0.3%; 95% CI 0.0-1.4), 16 (4.1; 2.4-6.6), 18 (4.7; 2.8-7.3), 15 (3.8; 2.2-6.2) with no epidural hematoma formation or bleeding into a critical organ.¹² The increase in bleeding was irrespective of surgical procedure and the composite endpoint of major and clinically significant bleeding showed similar results compared with the primary safety outcome. There was no further delineation or subcategorization of bleeding types.

Ginsberg et al¹³ performed a randomized, double-blind, active controlled, noninferiority study in patients undergoing total knee arthroplasty. Dabigatran 220 mg or 150 mg once daily, or enoxaparin 30 mg subcutaneously twice daily was administered at half dose 6 to 12 hours after surgery and/or full dose within 24 hours of surgery. Spinal anesthesia was utilized in 397 (46.3%) and 399 (45.8%) of cases with dosing of dabigatran at 220 or 150 mg, respectively. Spinal anesthesia was discontinued at the end of the surgery. Bleeding categories were outlined similarly to the study by Eriksson et al¹² previously discussed. Only 2 out of 5 and 3 out of 5 (for 220- and 150-mg dose, respectively) major bleeding events occurred. These were reported as bleeding at the surgical site and none required surgical intervention.¹³ There were no reported neuraxial-specific bleeding complications. Because of the lack of well-designed trials, the recommendations for management

of dabigatran is relegated to pharmacokinetics. For high-risk procedures including spine surgery, the recommendation is discontinuation 5 half-lives (4-5 days) prior to intervention. Resumption should begin at 24 hours after procedure and in high-risk individuals 12 hours may be an acceptable compromise. Of note, end-stage renal disease should discontinue dabigatran 6 days prior to intervention given its increased half-life of 28 hours in this population.

Rivaroxaban (Xarelto). Rosencher et al¹⁴ performed a randomized control trial comparing enoxaparin and rivaroxaban safety and efficacy in patients undergoing total knee or total hip replacement. Rivaroxaban 10 mg was started 6 to 8 hours after epidural catheter removal in 2489 patients undergoing neuraxial anesthesia. Rivaroxaban half-life is 5.7 to 9.2 hours and was held for 2 half-lives or 20 hours prior to epidural removal. There were no incidents involving epidural hematoma formation with this protocol. High-risk factors, including liver and renal disease were used as exclusion criteria. The lack of high-quality evidence relegates current recommendations to the pharmacokinetic profile of the drug.¹⁴ ASRA recommends 5 half-lives or 3 days withholding rivaroxaban prior to interventional spinal procedures. Resumption of lovenox is recommended at 24 hours postprocedure, or in high-risk individuals, half-dose at 12 hours may be an acceptable compromise.

The Heparins

Fondaparinux (Arixtra). Fondaparinux has been studied in 4 major clinical trials comparing to enoxaparin in thromboembolism prevention involving orthopedic surgery for hip and knee surgery. No study of therapeutic dosing exists within the spine surgery population.

Singelyn et al¹⁵ performed a prospective intervention study to evaluate safety and efficacy of neuraxial anesthesia in major orthopedic surgery in preventing thromboembolic complications. Daily 2.5 mg subcutaneous injections of fondaparinux were administered. The catheter was removed 36 hours after the last fondaparinux dose. After catheter removal the next fondaparinux dose was administered 12 hours later. Of 5704 patients a neuraxial catheter was inserted in 1553 (27%) patients. The remainder of the 5704 patients received deep peripheral nerve catheters. The incidence of major bleeding was 0.8% (42 of 5382) without any recorded epidural hematomas. These data demonstrated safe removal/manipulation of neuraxial anesthesia after only 2 half-lives of fondaparinux, corresponding to 25% of the drug still available.¹⁵ In the absence of high-quality data regarding therapeutic fondaparinux use in the spinal surgery population the safety and timing of therapeutic fondaparinux cannot be adequately assessed. For therapeutic fondaparinux, the recommendation of holding prior to surgery is relegated to the pharmacokinetic profile of the drug. Stopping fondaparinux 3 to 4 days prior to surgery will assure 97% drug elimination and is currently the ASRA guideline recommendation prior to neuraxial manipulation. Initiation

of fondaparinux is recommended to start at 24 hours post-surgery due to its quick onset of action of 1.7 hours.

Low-Molecular-Weight Heparin. The ARSA guideline recommendation is to withhold enoxaparin 12 hours for prophylactic and 24 hours for higher doses prior to neuraxial manipulation. This is predicated on data provided to the US Food and Drug Administration (FDA) Safety Communication released on November 6, 2013 by the manufacturer of enoxaparin, Sanofi-Aventis. They identified the following risk factors for epidural hematoma formation: ≥ 65 years of age, abnormalities of spinal cord or vertebral column, female sex, early postoperative administration (< 12 hours), patients at increased risk of hemorrhage, renal insufficiency, traumatic needle/catheter placement, indwelling epidural catheter during enoxaparin administration, twice daily administration (vs once daily administration), and simultaneous use of medications affecting hemostasis (eg, antiplatelet, anticoagulant, nonsteroidal anti-inflammatory drugs [NSAIDs]).¹⁶ The recommendation of 24-hour period between discontinuation and neuraxial manipulation corresponds to 5 half-lives assuring 97% of drug removal prior to intervention. After neuraxial procedures, the recommendation is 12 to 24 hours prior to resuming enoxaparin in higher risk patients. There is currently no available data regarding therapeutic enoxaparin and perioperative timing with regard to spinal surgery.

Heparin. Cain et al¹⁷ performed one of the only studies investigating therapeutic heparin use in patients undergoing spine surgery via a retrospective case series involving 22 members of the Scoliosis Research Society who were surveyed regarding their experience with therapeutic anticoagulation after pulmonary embolism. Inclusion criterion was pulmonary embolism within 14 days of thoracolumbar or lumbar spinal fusion. Of 13 000 patients, 9 met the above inclusion criterion. Anticoagulation was started at the timing of diagnosis of thromboembolic event, ranging from 1 to 14 days. Only 1 patient received therapeutic anticoagulation within 24 hours of surgery and suffered a wound hematoma. All epidural hematomas occurred on postoperative day 4 or later in 2 of the 9 patients.¹⁷ This study is limited by self-reporting of complications, lack of listed diagnostic criteria, and a small number of therapeutically anticoagulated patients. Current guidelines recommend stopping heparin within 4 hours of moderate- to high- risk surgery and resumption of therapeutic heparin 24 hours after surgery.⁶ If concern for coagulopathy remains, partial thromboplastin time (PTT) can be measured and protamine given at 1 mg per 100 U of heparin to reverse heparin prior to surgery. Heparin is considered therapeutic if activated PTT (aPTT) is 1.5 times or greater than then normal value. If any concern for heparin induced coagulopathy remains, checking the aPTT can help further guide decision making for reversal or postponing surgery in the case that it is not urgent or emergent.

Antiplatelet Agents

Atherosclerosis in the form of coronary artery disease and stroke represent leading causes of death worldwide. Antiplatelet agents such as acetylsalicylic acid (ASA) and clopidogrel (Plavix) block the thrombus formation cascade and halt vessel disease progression.¹⁸ Aspirin's effect is mediated via irreversible inhibition of cyclooxygenase 1 and 2 (COX 1 and 2) leading to inhibition of PGH₂, a precursor for TxA₂ formation responsible for platelet aggregation. Peak levels are reached within 30 to 40 minutes of administration, with a half-life of 20 minutes and the irreversible effect on COX1 maintains the antithrombotic effect for the life of the platelet (7-10 days).¹⁹ Clopidogrel is a thienopyridine that is converted to an active metabolite that binds P2Y₁₂ receptor in platelet and irreversibly inhibits it. Peak plasma concentrations are achieved at 30 minutes and dose dependent inhibition starts 2 hours after a single dose. It has a half-life of 7 to 9 hours. At steady state (days 3-7 of therapy), average inhibition level observed with a 75 mg Plavix dose is between 40% and 60%. These agents are part of the American Heart Association guidelines for prevention of strokes and management of myocardial infarctions and thus are widely used.^{20,21} Aspirin is recommended as lifelong therapy and clopidogrel is required for 6 weeks after placement of bare-metal stents, 3 to 6 months after myocardial infarction and usually 12 months after placement of drug-eluting stents. There are no specific guidelines from the manufacturer regarding perioperative management of antiplatelet agents; however, usually they are discontinued for 7 days prior to spine surgery if acceptable by cardiologist.

Aspirin. Cuellar et al²² retrospectively analyzed data from 200 patients with cardiac stents randomized to 100 of which underwent spine surgery while taking aspirin (81 or 325 mg) and 100 that underwent spine surgery after the institutional protocol guidelines of stopping it for 5 days prior to the operation. Variables analyzed included operative time, estimated intraoperative blood loss, postoperative transfusion of blood products, hospital length of stay, 30-day hospital readmission rate and reason, as well as intraoperative and postoperative complications. They demonstrated that patients who continued to take aspirin in the perioperative period had a hospital length of stay shorter than average (4.1 ± 2.7 vs 6.2 ± 5.8 days; $P < .005$) and a reduced operative time (210 ± 136 vs 266 ± 143 minutes; $P < .01$) without any significant difference in estimated blood loss (643 ± 905 vs 697 ± 1187 mL). Furthermore, the amount of blood products transfused, clinically significant spinal epidural hematomas, overall intra- and postoperative complication rate (8% vs 11%) and 30-day hospital readmission rate (5% vs 5%) were similar. There were no clinically significant spinal epidural hematomas observed in either branch of the study.²² There were more patients in the on-aspirin group taking 81 mg and more patients in the off-aspirin group taking 325 mg. This creates an inherent bias in the data; however there is significant evidence from the cardiovascular literature demonstrating no difference in clinical

effect of these 2 doses.²³ The study concludes that based on these data there is no major increase in perioperative variables aforementioned and most importantly no spinal epidural hematoma rate or occurrence rise with patients on aspirin. Stent thrombosis–related complications were not analyzed, despite observation that stopping these agents can risk a cardiovascular event especially in a prothrombotic environment such as spine surgery. Of note, this study included patients whose stents were placed on average 4 years prior to randomization, thus creating a low risk profile for stent thrombosis related complications. Soleman et al²⁴ performed a retrospective analysis of 102 patients undergoing non-instrumented extradural spine surgery (lumbar discectomy or laminectomy) divided into group taking ASA 100 mg daily (N = 40) and control group (N = 62). The study found no major difference in intraoperative blood loss ($P = .08$) or postoperative blood loss ($P = .76$). Both groups have similar hospitalization and operative times ($P = .28$, $P = .15$). The rate of cardiovascular complications and postoperative infections in the 2 groups showed no significant difference ($P = 1.0$).²⁴ Overall it states patients undergoing non-instrumented spine surgery are most likely safe to continue ASA treatment without leading to higher risk of morbidity, operative and hospitalization times.

Studies by Culler and Soleman demonstrated no evidence for increased risk in bleeding-related complications in spine surgery for patients on aspirin (81 or 325 mg), and potentially a therapeutic benefit from a cardiac standpoint in patients with stents. Kang et al²⁵ however performed a retrospective analysis of 76 patients undergoing spinal fusion for degenerative lumbar disease divided into 2 categories: those who had taken 100 mg ASA for an average of 40.3 months and stopped it prior to surgery for at least 7 days (N = 38) and a group that had not taken any aspirin. The groups were matched and underwent on average a 2-level spine fusion. The study discovered that the 2 groups had no significant difference in the estimated blood loss (855.3 vs 840.8 cm³, respectively) but there was a significant difference in blood drainage after the surgery (864.4 vs 458.4 cm³ in control group) ($P < .001$). The transfusion requirement postoperatively was greater in the ASA group ($P = .03$, $<.05$) and so was the postoperative rate of complications related to hemorrhage. The study concluded that although intraoperative blood loss was similar, ASA group even after stopping it for 7 days had a significant risk for higher blood loss and thus hemorrhage complications (including infection and epidural hematoma), thus inferring that aspirin should be stopped for more than 7 days, especially if major blood loss is anticipated.²⁵

Park et al²⁶ have published a series of studies discussing aspirin use and spine surgery. In 2013, a retrospective series was done to assess the proper discontinuation time frame of aspirin (100 mg) in spine (1-2 level) fusion surgery. The study was divided into 2 experimental groups: group 1 discontinued aspirin 3 to 7 days before surgery and group 2 discontinued it 7 to 10 days before surgery. Control group consisted of patients who did not use any aspirin before surgery (N = 96). The subcategories included 1-level posterior lumbar interbody

fusion (PLIF; no pedicle screw fixation) versus 1- to 2-level fusion procedures with interbody fusion and pedicle screw fixation. Data showed that total amount of drained blood (DB) and duration of indwelling of drain (DD) were significantly less in control group than in ASA group 1 undergoing either PLIF or 1-level PLIF + screw fixation ($P = .030$ and $P = .002$, respectively). There was no statistical significance in aforementioned variables between ASA group 2 and control group in either type of 1-level surgery. The drain amount was significantly less in control group in comparison to ASA group 1 in patients who underwent a 2-level fusion ($P = .0076$). There was no significant difference between groups in development of postoperative hematoma. The study concluded that if ASA is stopped 7 days or longer before spine surgery then there is no significant difference in bleeding risk compared with the ASA-naive control group.²⁶ To follow the above study, Park et al²⁷ published in 2014 a retrospective review of 106 patients who had undergone decompression and fusion on 2 segments were divided into 3 groups: not taking an antiplatelet agent (ASA 100 mg) before surgery (group 1, N = 38), taking it but discontinuing it a week prior to operation (group 2, N = 38) and taking it continuously just before the operation (group 3, N = 30). Amount of intraoperative blood loss, postoperative drain amounts and total blood losses ($P = .763$, $.175$, and $.192$, respectively) was not significantly different between groups. There were no epidural hematoma or infection complications reported. The study has NSAID administration as a confounding variable with increased blood loss; however, no homogeneous effect was seen among all 3 groups. The group concludes that ASA increases bleeding risk by using platelet function testing ($P < .05$) between groups 1 and 2 ($P = .029$) and between groups 1 and 3 ($P = .011$).²⁷

Most of this data is small population studies with confounding factors. There is variability across the board in the spine surgery population when it comes to aspirin use and surgical outcomes as well as bleeding complications. The overarching conclusion per ARSA guidelines states that surgery can be performed safely after 12 hours if low-dose ASA (<1 g) for secondary prevention, 3 days if ASA for primary prevention. This time is extended to 1 week if dose is >1 g/d. It may be reasonable to maintain patients on 81 mg ASA if extensive cardiac history (ie, cardiac stents that are drug eluding) as there are data suggesting continuing this drug can lead to fewer cardiac complications and these benefits could potentially far outweigh the risks of a surgical bleed major complication.

Plavix. McCunniff et al²⁸ performed a retrospective analysis in patients undergoing elective lumbar surgery, excluding known hypercoagulable states (eg, malignancy) or coagulopathies (eg, on warfarin). All patients stopped antiplatelet agents 7 days prior to surgery. No major bleeding complications occurred; however, there was increased blood loss in patients 7 days after cessation of antiplatelet agents. Clopidogrel was associated with 308.77 ± 285.37 versus 254.58 ± 185.03 cm³ per level of decompression blood loss in control group not on antiplatelet agents at baseline ($P = .04$, $<.05$). Additionally, clopidogrel

Table 1. Anticoagulation Agents and Their Half-Lives, Recommendation to Stop Based on Half-Life and Evidence Available to Support.^a

Spine Surgery Standard Anticoagulant Hold Times				
Listed Alphabetically by Generic Name				
Medication	When to Restart Postoperatively	Half-Life of Medication	Recommendations for stopping pre-op based on Half-Life	Evidence
Abciximab (ReoPro)			48 hours	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> . 2018;43:225-262
Apixaban (Eliquis) Prophylactic dose		8-15 hours	Consider 12-24 hours, but may be fine to NOT hold	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> 2018;43:225-262
Apixaban (Eliquis) Treatment dose		8-15 hours	2-3 days	Narouze S, Benzon HT, Provenzano D, 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, and the World Institute of Pain. <i>Reg Anesth Pain Med</i> 2018;43:225-262
Aspirin	7 days after	3 hours	5-7 days	Coleman JL, Alberts MJ. Effect of aspirin dose, preparation, and withdrawal on platelet response in normal volunteers. <i>Am J Cardiol</i> . 2006;98:838-841 doi:10.1016/j.amjcard.2006.03.071
Betrixaban (Bevyxxa)- Prophylactic dose [40-160 mg 4 times a day]		19-27 hours	1-2 days	Bevyxxa Package Insert Skellely JW, Thomason AR, Nolen JC, Candidate P. Betrixaban (Bevyxxa): A direct-acting oral anticoagulant factor Xa inhibitor. <i>Pharm Ther</i> . 2018;43:85-120
Cilostazol (Pletal)		10 hours	2-3 days	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> . 2018;43:225-262 Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. <i>Chest</i> . 2012;141(2 suppl):e326S-e350S. doi:10.1378/chest.11-2298
Clopidogrel (Plavix)		6 hours	5-7 days	Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. <i>Circulation</i> .

(continued)

Table 1. (continued)

Spine Surgery Standard Anticoagulant Hold Times				
Listed Alphabetically by Generic Name				
Medication	When to Restart Postoperatively	Half-Life of Medication	Recommendations for stopping pre-op based on Half-Life	Evidence
Dabigatran (Pradaxa)		Creatinine clearance (CrCl) >80 mL/min ($t_{1/2} \sim 14$ hours) CrCl 50-80 mL/min ($t_{1/2} \sim 17$ hours) CrCl 30-49 mL/min ($t_{1/2} \sim 19$ hours) CrCl 15-29 mL/min ($t_{1/2} \sim 28$ hours)	3 days 4 days 4 days 6 days	2004;110:1202-1208. doi:10.1161/01.Cir.000.140.675.85.342.1b Benzon HT, McCarthy RJ, Benzon HA, et al. Determination of residual antiplatelet activity of clopidogrel before neuraxial injections. <i>Br J Anaesth.</i> 2011;107:966-971 doi:10.1093/bja/aer298 Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> 2018;43:225-262 Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. <i>Clin Pharmacokinet.</i> 2010;49:259-268
Edoxaban (Savaysa) Treatment dose [30-60 mg daily]		8-14 hours	2-3 days	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> 2018;43:225-262 Lip GY, Agnelli G. Edoxaban: a focused review of its clinical pharmacology. <i>Eur Heart J.</i> 2014;35:1844-1855.
Enoxaprin (Lovenox) Prophylactic dose [30 mg twice daily or 40 mg 4 times a day]	Next scheduled dose	4-7 hours	Consider 12-24 hours, but may be fine to NOT hold	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> 2018;43:225-262
Enoxaprin (Lovenox) Treatment dose [>40 mg 4 times a day]		4-7 hours	24 hours	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> 2018;43:225-262

(continued)

Table 1. (continued)

Spine Surgery Standard Anticoagulant Hold Times				
Listed Alphabetically by Generic Name				
Medication	When to Restart Postoperatively	Half-Life of Medication	Recommendations for stopping pre-op based on Half-Life	Evidence
Eptifibatide (Integrilin)			4-8 hours	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> . 2018;43:225-262
Fondaparinux (Arixtra) Prophylactic dose [<2.5 mg daily]		17-21 hours	Consider 24-36 hours, but may be fine to NOT hold	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> . 2018;43:225-262 Bauer KA. Fondaparinux: basic properties and efficacy and safety in venous thromboembolism prophylaxis. <i>Am J Orthop</i> . 2002;31:4-10 Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. <i>N Engl J Med</i> . 2001;344:619-625
Fondaparinux (Arixtra) Treatment dose [>2.5 mg daily]		17-21 hours	4-5 days	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med</i> . 2018;43:225-262 Bauer KA. Fondaparinux: basic properties and efficacy and safety in venous thromboembolism prophylaxis. <i>Am J Orthop</i> . 2002;31:4-10 Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. <i>N Engl J Med</i> . 2001;344:619-625
Heparin Prophylactic dose [5000 u every 8 hours]	Next scheduled dose	1-2 hours	Consider 4-6 hours, but may be fine to NOT hold	Horlocker TT, Vandermeulen 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). <i>Reg Anesth Pain Med</i> 2018;43:263-309. doi:10.1097/aap.0000000000000763
Heparin Treatment dose [intravenous drip]		1-2 hours	4-6 hours (activated partial thromboplastin time [aPTT] <35.7 s)	Horlocker TT, Vandermeulen 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). <i>Reg Anesth Pain Med</i> . 2018;43:263-309. doi:10.1097/aap.0000000000000763

(continued)

Table 1. (continued)

Spine Surgery Standard Anticoagulant Hold Times				
Listed Alphabetically by Generic Name				
Medication	When to Restart Postoperatively	Half-Life of Medication	Recommendations for stopping pre-op based on Half-Life	Evidence
Other nonsteroidal anti-inflammatory drugs (NSAIDS)	7 days after	Variable	Consider 5-7 days, but may be fine to NOT hold	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med.</i> 2018;43:226-252.
Prasugrel (Effient)			7-10 days	Asai F, Jakubowski JA, Naganuma H, et al. Platelet inhibitory activity and pharmacokinetics of prasugrel (CS-747) a novel thienopyridine P2Y12 inhibitor: a single ascending dose study in healthy humans. <i>Platelets.</i> 2006;17:209-217. doi:10.1080/09537100600565551
Rivaroxaban (Xarelto) Treatment dose [>10 mg 4 times a day]		9-13 hours	2-3 days	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med.</i> 2018;43:225-262 Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. <i>Br J Clin Pharmacol.</i> 2010;70:703-712. doi:10.1111/j.1365-2125.2010.03753.x
Rivaroxaban (Xarelto®) Prophylactic dose [10 mg 4 times a day]		9-13 hours	Consider 12-24 hours, but may be fine to NOT hold	Narouze S, Benzon HT, Provenzano D, 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. <i>Reg Anesth Pain Med.</i> 2018;43:225-262 Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. <i>Br J Clin Pharmacol.</i> 2010;70:703-712. doi:10.1111/j.1365-2125.2010.03753.x
Ticagrelor (Brilinta®)			5 days	Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. <i>Circulation.</i> 2009;120:2577-2585. doi:10.1161/circulationaha.109.912550
Ticlopidine (Ticlid)			10-14 days	Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. <i>Chest.</i> 2012;141(2 suppl):e326S-e350S. doi:10.1378/chest.11-2298. Ticlid Package Insert

(continued)

Table 1. (continued)

Spine Surgery Standard Anticoagulant Hold Times				
Listed Alphabetically by Generic Name				
Medication	When to Restart Postoperatively	Half-Life of Medication	Recommendations for stopping pre-op based on Half-Life	Evidence
Tirofiban (Aggrastat)		1-1.5 hours	4-8 hours	Narouze S, Benzon HT, Provenzano D, et al. <i>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</i>
Vorapaxar (Zontivity)		3-4 days	12-20 days	Abdulsattar Y, Ternas T, Garcia D. Vorapaxar: targeting a novel antiplatelet pathway. <i>Pharm Ther. 2011;36:564-568</i>
Warfarin (Coumadin)		40 hours	5-6 days, (international normalized ratio [INR] ≤ 1.5)	Narouze S, Benzon HT, Provenzano D, et al. <i>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.</i>

^aSurgical team recommendations take precedence over these standard times if different. Surgeons/APPs (advanced practice providers) are responsible for initial communication of this to patient and coordination with Spine Program Manager to ensure consistent messaging. Spine Program Manager will communicate changes to RT4 Manager.

had 444.39 ± 239.42 versus 447.83 ± 312.06 cm³ per level of fusion blood loss and 447.88 ± 249.97 versus 512.77 ± 332.66 cm³ per level of instrumentation blood loss ($P < .01$).²⁸

Akhavan-Sigari et al²⁹ published a prospective cohort of 100 patients undergoing spinal surgery without discontinuation of aspirin or clopidogrel due to medical contraindication for antiplatelet discontinuation. Sixty-three patients were on both clopidogrel and ASA and 37 on ASA only. No major bleeding complications and no neurological sequelae related to bleeding occurred. Case length was increased in 22 of 41 combined anterior-posterior surgeries. 6 subcutaneous hematomas, 3 postoperative wound dehiscence, and 1 wound infection occurred.²⁹

Benzon et al³⁰ analyzed 13 patients on clopidogrel or clopidogrel plus aspirin undergoing epidural steroid injection. Inhibition of platelet function by clopidogrel was measured by platelet-induced aggregation as platelet reaction units (PRUs) and antiplatelet effect of clopidogrel after discontinuation was evaluated with a platelet function analyzer (PFA-100). There was no significant difference in the PRUs or PFA-100 results between days 5 and 7 of discontinuation. This small study supports a 5-day discontinuation of clopidogrel monotherapy or dual antiplatelet therapy is as safe as waiting 1 week.³⁰ In accord with the ARSA guidelines for antiplatelet discontinuation, surgery can be performed safely after 5 days

off of clopidogrel. When in doubt, platelet function assays may be utilized to determine residual drug effects since as many as 30% of patients may be nonresponders or partial responders.³¹

Discussion

Warfarin discontinuation is commonly practiced and if absolutely contraindicated, a heparin bridge can be used with titration of PTT to levels in which the surgeon is comfortable operating without significantly increasing the chance of a thromboembolic event.

For Xa inhibitors or novel oral anticoagulants (NOACs) it seems that an individualized approach to each patient should be taken. Most recommendations are reduced to their pharmacokinetic profile with 5 half-lives recommended for all new Xa inhibitors or NOACs. Should this be deemed an unacceptable delay in care or surgery is urgent, one can use prothrombin complex concentrate for reversal of dabigatran. A more novel therapy is the antidote idarucizumab, which has been shown to adequately reverse its effects.³² For apixaban and rivaroxaban prothrombin complex concentrate has been effective.³³ For resumption of Xa inhibitors after surgery, most guidelines recommend 24 hours. The ARSA has a half-dose regimen for high-risk patients that may be a safe compromise in certain high-risk patients for thromboembolic complications. Half-

therapeutic dosing at 12 hours postoperatively may be a safe option for high risk patients and should be considered on a case by case basis.

For the heparin agents, it is recommended that LMWH be held for 12 to 24 hours, ensuring 97% or more of the drug has been metabolized before a procedure. Heparin needs to be stopped usually at least 4 hours prior to surgery for normalization of PTT. If urgent surgery is needed, 1 g of protamine can be given for every 100 units of heparin administered in the past 2 to 3 hours with a maximum dose of 50 mg.

For antiplatelet agents, full-dose Plavix should be stopped for 5 to 7 days. ASA can be stopped for 1 to 3 days prior to operation depending on reason for drug and must be stopped for 1 week for doses >1 g/d. There is evidence that 81/100 mg aspirin daily does not increase bleeding risk.

In the absence of high-quality data for discontinuation and resumption of anticoagulation agents, the aforementioned results can provide us with some insight into the standard practiced guidelines for different agents. Table 1 is a comprehensive list of the most popular anticoagulation agents as well as their half-lives, and evidence available to suggest peroperative management in spine surgery.

Limitations and Future Study

This review was limited due to the lack of literature available. The specific consideration of therapeutic anticoagulation in spine patients is especially difficult to investigate because of the fact that most guidelines are based on metabolism of drugs and little data on risks of anticoagulation related to postoperative complications. Moreover, these studies are largely retrospective and due to this are inherently biased. Further studies with multicenter clinical randomized control trials would need to be done, although this is likely to be deemed unsafe by ethical standards. Another flaw of this review is that studies were selected for therapeutic anticoagulation; however, often prophylactic use of same drugs are described in the studies. Because of the broadness of the topic, we attempt to exclude most of these articles to provide most relevant information to the topic at hand. Finally, there is an ethical dilemma in creating a study of spinal surgery while therapeutically anticoagulated. The potential consequences of a fully anticoagulated patient undergoing spinal surgery makes the creation of such a study exceedingly difficult to perform in a prospective manner.

Conclusion

Therapeutic anticoagulation use in spine surgery is a challenging topic due to the need to balance possible catastrophic consequences of withholding anticoagulation against the possible risks related to postoperative complications. The current guidelines are largely based on drug metabolism but do provide a reliable measure to establish drug effect in this patient population. Little to no data exists on risk of surgically managing spine conditions in these patients. Further randomized

controlled trials would be needed. This review identifies major anticoagulants and current guidelines for management in perioperative period.

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