Too Thin? Hip Fracture in a Patient on Anticoagulation. A Review of Novel Oral Anticoagulation Therapy

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Stem Case and Key Questions Content

85-year-old, 50kg man presenting for left hip hemiarthroplasty after he fell in his apartment two days ago. His past medical history includes hypertension, atrial fibrillation, cerebral vascular event with minimal neurologic deficits, osteoarthritis, and chronic renal insufficiency. His medications include aspirin 81mg, metoprolol 50mg, and dabigatran 150 mg BID. The last time he has taken aspirin and dabigatran was 55 hours ago. His hematocrit is 25, creatinine is 1.8, and INR is 1.2. The cardiologist documented that patient is cleared for surgery.

1. Is further workup necessary for this patient before proceeding with the procedure?

2. What are the anesthetic options for this patient? Is a neuraxial technique acceptable?


4. What are the other novel oral anticoagulants that are available on the market? What is the FDA approved indications for these? What do the clinical trials shown about their efficacy?

5. How does this patient’s weight and renal clearance affect the timing of the surgery and anesthetic?

6. How do we calculate renal clearance?

7. What is the current guideline regarding neuraxial anesthesia with patients on novel oral anticoagulant such as rivaroxaban?
8. How should we decide on transfusion? Should we transfuse preoperatively?

9. What other considerations are there for blood conservation management? Discuss efficacy of iron or erythropoietin stimulating agents (ESA), blood salvage devices, or antifibrinolytic therapy.

10. How would you stratify the patient’s risk for this procedure? What discussion would you have with the surgeon in terms of surgical time and techniques?
Blood bank notified you that an earlier type and crossmatch sample was lost and a new sample obtained 2 hours ago revealed antibodies. Meanwhile, patient is complaining of severe pain in the left hip. He is hemodynamically stable and he is NPO.

11. How does anemia and transfusion contribute to perioperative complications?

12. How long would you postpone the procedure for? Would you consider O negative blood?

13. What analgesia options do you have preoperatively?

14. How do you perform an ultrasound guided fascia iliaca block? Have they shown to be efficacious in this setting?

15. Would you place a continuous indwelling fascia iliaca catheter?

16. Briefly summarize the current recommendation on peripheral nerve blocks in an anticoagulated patient.
The surgery proceeds and surgeon informs you that they lost 1L of blood acutely during prosthesis insertion and they are having difficulty with hemostasis. They want to consult you about reversing residual anticoagulation effects.

17. What are effective reversal regimen for dabigatran and other novel anticoagulants? What is substantiated from animal and human clinical models?

18. What additional laboratory monitoring do you need to confirm coagulopathic diagnoses? Discuss utility of the following: coagulation profile, thrombin time, bleeding time, TEG.

19. How does this affect your postoperative DVT prophylaxis management?
Model Discussion Content

Spinal hematoma remains the most concerning and catastrophic adverse event that can occur in patients receiving neuraxial anesthesia. Since 2010, newer anticoagulants have gained widespread use for treatment and prevention of venous thromboembolism (VTE), atrial fibrillation (AF), and acute coronary syndrome. Despite the increased use of these novel anticoagulants, guidelines pertaining to regional anesthesia remain limited. ASRA has recently started updating its guidelines based largely on the pharmacokinetic properties. In general, an elimination period of 5 half-lives, or 97% clearance of the drug, is considered an acceptable time lapse after drug cessation to allow for safe performance of neuraxial techniques without an increased bleeding risk. Selective emerging novel oral agents, with implications for regional anesthesia are highlighted below.

Rivaroxaban (Xarelto) is an factor Xa inhibitor. Its peak effect is 2.5-4 hr. With a half life of 5-9 hr in a healthy person (CrCl>50 ml/min), 5 half-lives would be 2-3 days. In elderly patients the half-life is 9-13 hr making 5 half-lives around 4 days. There is an increased plasma concentration of up to 24% in patients weighing less than 50 kg. Clearance is mainly fecal/biliary (66%) and renal (33%). Resumption of drug after indwelling catheter is 5.5-21.5 hr depending on clearance. Monitoring can be done by checking anti-factor Xa assay. It can be reversed with Prothrombin Comlex (PCC) Apixaban (Eliquis) is also a factor Xa inhibitor. Its peak effect takes place at 1-2 hr and it has a half life of 15 hr. Clearance is 25% renal and 75% fecal/biliary and five half-lives is approximately 3-4 days with CrCl >50 ml/min and 4-5 days with CrCl 15-50 ml/min. Resumption of drug after indwelling catheter removal is 7-23 hr. Monitoring can be done by checking Anti-Factor Xa assay or with PT diluted with laboratory reagent.

Dabigatran (Pradaxa) is a direct thrombin inhibitor. Its peak effect takes place at 2 hr and has a half-life of 12-14 hr in healthy patients, 14-17 hr in the elderly, and 28 hr in ESRD. Clearance is 80% renal and 20% fecal. Plasma concentration can be 50% higher in elderly versus young and low body weight could be a risk factor for bleeding. Five half lives is strongly dependent on creatinine clearance. It takes approximately 3-4 days with CrCl >50 ml/min, 4-5 days with CrCl 30-50ml/min, and 6-7 days with ESRD. Resumption of drug after indwelling catheter removal is 6-22 hr. Monitoring can be done by checking thrombin time and it can only be reversed with hemodialysis.

Prasugrel (Effient) is an antiplatelet P2Y12 receptor inhibitor. It has 90% platelet inhibition vs. 60% for clopidogrel. Its peak effect is 1 hr. Unlike the other agents, it is not affected by moderate renal or hepatic dysfunction. It has a half-life of 3.7 hr however, it can take 7-10 days to reverse platelet inhibition and is dependent on platelet turnover. Resumption of drug after indwelling neuraxial catheter removal is 24 hr. Monitoring can be done by checking P2Y12 assay, Thromboelastography (TEG) or multiple electrode platelet aggregometry.

Ticagrelor (Brilinta) is an antiplatelet reversible ADP analogue on P2Y12 receptor. Its peak effect is 2-4
hr and is dependent on platelet turnover for clearance. European labeling suggests 7-day cessation before surgery. Clearance is mainly through the liver but hepatic dysfunction does not affect platelet inhibition. Resumption of drug after indwelling neuraxial catheter removal is 24 hr. Monitoring can be done by checking P2Y12 assay, TEG, or multiple electrode platelet aggregometry.

As with many complex clinical decisions, an informed dialogue between the patient and the perioperative team regarding the benefits and risks of anticoagulation management is essential to ensure positive outcomes. Interdisciplinary and timely preoperative coordination between anesthesiology, surgical, cardiology, and medicine teams is crucial to enhance patient safety. The most challenging dilemma is balancing the risks of thromboembolism against neuraxial and surgical bleeding. The decision to cease anticoagulation to allow for safe neuraxial anesthetics and surgery requires assessment of the patient's thromboembolic risk factors, indications for anticoagulation therapy, anticoagulant pharmacokinetics, surgical bleeding risk, and other patient characteristics. Basic postoperative measures to reduce the incidence of neuraxial bleeding include minimizing traumatic neuraxial techniques, altering postoperative anticoagulant initiation with traumatic neuraxial anesthetics, avoiding indwelling neuraxial catheters or adjusting the timing of the removal of indwelling catheters.

The first step to risk stratification is determining reasons for anticoagulation and risk of thrombosis. Differentiating between primary and secondary prevention and treatment of existing thrombotic complications is useful in determining baseline risk. For instance, prevention of stroke in a patient with a single episode of paroxysmal atrial fibrillation (AF) is significantly different than a patient with multiple comorbidities such as advanced age, recent VTE, stroke, ACS, mechanical heart valves or longstanding AF. The American College of Chest Physician 2012 guidelines on perioperative management of antithrombotic therapy and a substantiated scoring system such as CHADS2 may be helpful to categorize these risks.

Another consideration during risk evaluation is patient physiological impact on the pharmacokinetic properties of anticoagulants. Patient characteristics such as anemia, thrombocytopenia, and concomitant administration of NSAIDS or other antiplatelet agents can influence the metabolism of anticoagulants. More importantly, renal metabolism most likely accounts for the prolongation of drug half-lives due to age and body weight reported in clinical trials. For instance, the half-life of rivaroxaban is 5-9 hours in healthy volunteers and 9-13 hours in elderly patients. The half-life of dabigatran doubles to 28 hours in ESRD patients and is contraindicated for severe renal dysfunctional patients in Europe. Since creatinine clearance reflects age, weight, and renal function, it is a vital parameter to integrate into the decision for the cessation of anticoagulants.

As we wait for specific American guidelines, it appears prudent to wait at least 3-4 half-lives following anticoagulant cessation in high risk patients, prior to a neuraxial anesthetic. Alternatively, longer
cessation intervals (such as 5 half-lives in patients with low risk for thrombosis) may be appropriate. Although this approach seems clinically sensible, more prospective evidence is needed to evaluate efficacy and safety. For now, individual practitioner judgment, comprehensive insight of creatinine clearance based anticoagulant pharmacology, and sound clinical reasoning that tailors to patients characteristics should prevail.

In patients with neuraxial catheters requiring novel oral anticoagulants after surgery, there are two major decisions: when to remove the catheter and when to restart anticoagulation. Most experts agree that removal of the catheter should coincide with a reasonably safe plasma concentration of the anticoagulant. Rosencher et al. advocates at least two half-lives to pass before catheter removal believing that 25% of the original drug concentration is a reasonable compromise between thrombosis and bleeding. Since clearance starts to plateau after two half-lives, waiting longer would not decrease drug concentration by a significant amount. However, clearance may be unpredictably prolonged in patients with renal impairment. So far, no specific clinical updates or validated studies have provided insights to proceeding with catheter removal in patients with renal dysfunction. Despite the theoretical safety proposed by Rosencher et al., it may be prudent to avoid indwelling catheters or follow the same guidelines as for catheter insertion when anticoagulation is to be used postoperatively. This data is based only on postoperative prophylactic dosing of the newer anticoagulants. However, it is important to recognize that this anticoagulation profile may be based on a healthier clinical study population where subjects with extremes of age, renal impairment (CrCl<30 ml/min), concomitant antiplatelet therapy, and lower body weight were excluded.

For resumption of anticoagulation, Rosencher et al. offered an 8 hour model of platelet plug formation and stability as a basis for his recommendations. Benzon et al. agreed that hemorrhage models in cerebral embolism with thrombolitics or intracranial bleeding with enoxaparin suggest that anticoagulants do not appear to disrupt clots once they are stable after 8 hours. Still, conservative experts advised waiting 24 hours (up to 48 hours in patients with high risk of bleeding) after surgery to avoid excessive perioperative surgical bleeding. More research and evidence are needed to address the safety of the timing regimen. As for now, the period of resumption of anticoagulation ranges from 8 hours, minus the peak effect time of the anticoagulant, to 48 hours after surgery for patients at high risk of bleeding.

There is no definitive antidote with proven efficacy for the novel oral anticoagulants. Potential agents are inconsistent in their abilities to reverse coagulation parameters, clinical bleeding, and mortality outcomes in animal studies. Activated charcoal within the first 2 hours of anticoagulant ingestion, subsequent resuscitation of massive bleeding, and interventions to achieve hemostasis remain the cornerstone of treatment for the hemorrhagic patient requiring emergency surgery.

There are some prospective reversal agents which may be beneficial with certain agents. Prothrombin
complex concentrates (PCCs) may have thrombotic risks and there is no human data with clinical bleeding. With rivaroxaban it corrected coagulation laboratory parameters in humans (50IU/kg) but did not reduce clinical bleeding in animal studies. The data is inconclusive with dabigatran. Hemodialysis can be used with dabigatran and can remove 60%-70% in 2-4 hours however, it may be challenging to establish emergent dialysis in hemorrhagic shock. It is not useful with Rivaroxaban and Apixaban as they are highly protein bound drugs. There is no data regarding FFP. Platelets can provide non-affected platelets after thienopyridines. Recombinant factor VIIa poses a significant risk of thrombosis and animal and laboratory data are inconsistent and inconclusive. There is a dabigatran neutralizing antibody that is in development.

In the 2010 recommendation, ASRA suggested that all peripheral nerve blocks follow the same anticoagulation precautions as neuraxial anesthesia. It is important to note that this suggestion was made as a general agreement of efficacy based on case reports of 26 patients and expert opinion. Of the 26 case reports, 13 involved patients receiving anticoagulation reported complications. 9 of the complications involved deep plexus blocks including paravertebral, sciatic blocks, and interventional pain procedures. Serious complications associated with deep plexus blocks involved mainly hemorrhagic events and no permanent neurological deficits. The remaining 4 blocks include continuous femoral catheters combined with sciatic catheters, fascia iliaca block, and serial intercostal blocks that resulted in bleeding requiring blood transfusion.

The authors of ASRA guidelines did acknowledge that there is insufficient evidence to associate peripheral plexus techniques with hemorrhagic or neurologic complications. Also, they recognized that a large number of interventional cardiology procedures are performed with intravascular catheterization in patients receiving anticoagulation that did not result in high incidence of complications. Moreover, they quoted a study of continuous lumbar plexus catheter in 670 patients with only a single event of local bleeding. It is therefore controversial whether case reports merit such a definitive equivalency between superficial plexus, deep plexus, and neuraxial techniques. Based on the case reports, it would appear that superficial plexus blocks are unlikely to result in catastrophic complications in patients on anticoagulation.

Not all experts around the world agree on the same recommendations. The European society of anesthesia guidelines states that, “complications of peripheral nerve blocks are less serious than central neuraxial blockade… Existing guidelines for neuraxial blockade do not routinely apply.” The Austrian society made specific distinctions on superficial versus deep and neuraxial blocks and suggested that superficial blocks may be performed with caution in patients receiving anticoagulants. Overall, peripheral blockade with anticoagulation remains a contentious issue for experts in regional anesthesia due to knowledge gaps and lack of evidence.

Major joint replacement, such as knee or hip, offers the greatest risk of VTE. Anticoagulation is
usually started on the day of surgery as prophylaxis to VTE. Current recommendations as per the American Academy of Orthopedic Surgeons offer a variety of options depending on the clinical situation. Other options for VTE prophylaxis include twice daily dosing of aspirin, low molecular weight heparin, warfarin, synthetic pentasaccharides, or only mechanical compression devices.

According to the American Academy of Orthopedic Surgeons (AAOS) a risk stratification based on risk of PE vs major bleeding will help determine the level of chemoprophylaxis for DVT and if it is even necessary. Judgment should be used on a case to case basis.

A large prospective study done by Bierbaum et al from The Journal of Bone and Joint Surgery showed that amongst patients who received total knee or hip arthroplasty, 46% required blood transfusion. However, the majority of those did not receive allogenic blood. The options for blood conservation are greater in an elective procedure with a known significant blood loss. A plan can be set in place well in advance of the surgery and the safest options for the patient can be implemented. In a more acute setting there are fewer options.

Allogenic blood transfusions are the most readily available in the acute setting. However, it is associated with all the risks associated with blood transfusion including infection, lung injury, and transfusion reactions. Autologous blood donation requires preparation in advance and careful selection of candidates. There is still a risk for laboratory error.

Autologous blood cell salvage cannot be used in all situations. It is often set up in advance if there is significant anticipated blood loss. If there is a coagulation or platelet dysfunction, cell salvage will return the defected blood to the patient.

Acute normovolemic hemodilution can also be done. By adequately replacing blood with crystalloid fluid the blood loss during the surgery contains less red cells and coagulation content. Often up to 1 L is taken off. It can be returned to the patient when needed.

In certain cases erythropoietin stimulating agents (ESA) can be used. Recent guidelines from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists from 2011 include an EPO plus iron course for certain patients prior to cardiac surgery. It is not for use in all cases as EPO has a boxed warning stating an increased risk of mortality, myocardial infarction, stroke, and thromboembolism. Also, the manufacturer states that there is an increased incidence of deep venous thrombosis among patients receiving EPO and undergoing orthopedic surgery.

Anesthetic technique may also assist with decreasing blood loss. Normothermia has been associated with less blood loss. Controlled hypotension and proper fluid replacement may also play a positive role. Also, an antifibrinolytic agent is often used to decrease surgical bleeding.
In 2009, a review of randomized trials regarding antifibrinolytic therapy in orthopedic surgery demonstrated a significant decrease in blood loss and need for blood transfusion with use of an antifibrinolytic agent. More importantly, there was no increase in risk of thromboembolic events. Care must be taken though in patients who have active intravascular clotting or a history of thromboembolic events.

A fascia iliaca block blocks the femoral and lateral femoral cutaneous nerves as they pass beneath the fascia iliaca. It is a simple regional technique for analgesia for lower extremity procedures. Studies are mixed regarding the efficacy in pain relief when compared to a femoral nerve block, however, all are in agreement that it is beneficial when compared to standard opioid therapy. A recent study in hip fracture patients strongly demonstrated the effectiveness of a fascia iliaca block with preoperative pain relief as well as improved ability to maneuver the patient for placement of neuraxial anesthesia and positioning on the operating room table.

Typically this block is done under ultrasound guidance. Lateral to the femoral artery, the iliopsoas muscle is identified with the fascial plane overlying it. An in-plane approach is typically used and once the needle is identified in the proper position a deposit of 30-50 mL of local anesthetic is injected.

References
7. Rodgers et al Reduction of postoperative mortality and morbidity with epidural or spinal anesthesia: Results from overview of randomized trials. BMJ 2000;321:1493