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A Slip and Fall in the Post Warfarin Era

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Stem Case and Key Questions Content

You are the anesthesia provider at a local community hospital. Your next patient is an 84 year old 160cm, 108 kg female who fell while reaching for an object in her bathroom. She is scheduled for operative repair of right femoral head fracture. Upon initial evaluation of the patient, you note that she has a short thick neck and a class 3 airway, redundant neck tissue, with large tongue and limited mouth opening. Her past medical history is notable for coronary artery disease, diabetes mellitus type II, and atrial fibrillation. Vital signs are within normal limits. She is appropriately nil per os.

1. What are your perioperative concerns in this patient?

2. What is your anesthetic plan for this case?

3. Are you concerned about this patient's airway? Specify your plans for induction and airway management.

4. Would you like to have any labs or test results? If so which ones and why?

5. What information about this patient's past medical or surgical history are you interested in? Why?

You speak to the patient and her husband in the pre-op holding area. She endorses a history of atrial fibrillation, diagnosed 7 years ago due to intermittent chest pain. She is also a diabetic, with well controlled blood sugars although she is not always compliant with her medication regimen. Labs are unremarkable with a starting hematocrit of 38, creatinine 1.0, blood glucose 210mg/dl. Echocardiogram is notable for left atrial enlargement, ejection fraction of 60%. Patient denies tobacco or alcohol abuse. She has 2 units of packed red blood cells available.

6. Do you need any more information before taking this patient to the OR? If so, what and why?

7. Does her history of diabetes affect your perioperative management plan? If so, how?

Other medical history includes hypertension, hyperlipidemia, gastro-esophageal reflux disease, obstructive sleep apnea, chronic low back pain, fibromyalgia, prior stroke (no residual deficits), and a remote history of bare metal stent placement for coronary artery disease. Medication list includes dabigatran, aspirin, simvastatin, lisinopril, pregabalin, oxycodone, glyburide, metformin,

and celecoxib.

8. Discuss the pros and cons of regional versus general anesthesia for this patient.

9. What is dabigatran? Does her use of dabigatran constitute an absolute contraindication to a regional technique? Does it alter your anesthetic plan?

10. Describe your perioperative management plan for this patient's anticoagulants.

11. What is your plan for perioperative pain control?

The patient's prior anesthetic records are reviewed. She was easily mask ventilated and intubated via C-MAC blade, 6 months ago for a blepharoplasty. You decide to proceed to the operating room where you successfully induce and intubate her. Forty five minutes later, the surgeon complains that the patient is "oozy" and blood loss now totals more than 1500ml with a decrease in hematocrit to 23. Vitals: heart rate 121, electrocardiogram without S-T changes, blood pressure 87/45, oxygen saturation 98% on 50% oxygen.

12. Do you transfuse? If so, what blood product(s) would you give? Is there a role for Factor 7 in this scenario?

13. What are your plans for resuming anticoagulation postoperatively?

Model Discussion Content

Perioperative management of anticoagulants is a common clinical problem. As the United States' population ages, the total number of individuals with disorders that require anticoagulant use is expected to rise rapidly. The most common indications for perioperative anticoagulation are atrial fibrillation, prior venous thromboembolic event, and mechanical heart valve. Surgery is thought to increase VTE risk 100-fold and may increase risk of post procedure thromboembolic events1, 2. Risk factors for blood clot formation include orthopedic surgery, vascular surgery, head and neck cancer surgery and surgical time greater than forty five minutes 1.

Due to the increased perioperative risk of bleeding and blood transfusions, approximately 25% of patients with atrial fibrillation who are anticoagulated will require interruption for invasive procedures every year 3. Cessation of these agents places patients at higher risk of deep vein thrombosis and embolic phenomena after major surgery 1. Perioperative management requires the clinician carefully balance risk of bleeding and risk of thrombus formation 4. Given these considerations, it is imperative that the anesthesiologist become comfortable with management of anticoagulants in the perioperative period.

In the past, periprocedural management of patients with atrial fibrillation, VTE history or mechanical valves has involved use of agents such as heparin, low molecular weight heparin (ie enoxaparin), and warfarin. As our experience with these medications has grown, so has knowledge of their limitations. Specific drawbacks of older anticoagulants include delayed onset of action, resistance, hypersensitivity, need for frequent lab draws, and variable pharmacologic profiles 5.

Novel anticoagulant agents (NOCs) were born out of a need to address some of the problems listed above. In the past three to five years, studies have shown these NOCs to be more convenient for the patient to use; additionally they have been shown to be equivalent (and in some cases superior to) warfarin and enoxaparin for VTE prophylaxis6. Given decreased patient burden and advantages such as a more rapid onset of action, shorter half-lives, fewer drug-drug interactions, less need for routine lab draws and more desirable pharmacokinetic properties, use of the NOCs have skyrocketed 1, 3,4,6,7. Patients with VTE are treated with anticoagulants for approximately three months while those diagnosed with atrial fibrillation or implanted with a mechanical valve can expect a treatment period lasting months to years··· ..sometimes a lifetime6. Unlike older agents, rapid onset and offset of these anticoagulants also obviate the need for perioperative bridging reducing cost, risk and inconvenience for the patient 1.3. Unfortunately, there is very little data to guide the dilemma of appropriate timing of discontinuation and re-initiation of these NOCs perioperatively.

Direct Thrombin Inhibitors (DTIs): Dabigatran is the prototype drug in this class. The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial compared efficacy of warfarin to dabigatran and showed the DTI to be equally well tolerated and more effective at preventing stroke and embolic phenomena in patients with atrial fibrillation3. When compared to warfarin, dabigatran has a more rapid onset of action with peak effect occurring within 3 hours of oral intake1. Its primary function is to inhibit the final step of the coagulation cascade thereby prevention conversion of fibrinogen to fibrin. Approximately 80% of this drug is renally excreted and it has a half-life of 12-14 hours therefore it should be avoided or very cautiously dosed in patients with impaired renal function 7. The appropriate time to discontinue dabigatran prior to elective surgery is dependent on multiple factors including: elimination half-life, patient's renal function, anesthetic technique as well as surgical risk1. In general, a period of time totaling 4-5 half-lives is appropriate to ensure minimal residual anticoagulant effect. A suggested approach for perioperative management of DTI's is outlined in Table 1. The patient's bleeding risk should also be assessed and the DTI's rapid onset of effect should also be taken into consideration 1. Though dabigatran is now commonly used to manage embolic risk associated with atrial fibrillation, major concerns regarding use of medications from this class remains. For example, there are no antidotes or reversal agents available for DTIs at this time and their clinical effects are difficult to measure 3. A dilute thrombin assay (Hemoclot test, available outside the United States) shows promise as an accurate test of residual dabigatran and may be utilized perioperatively. Alternately, an activated partial thromboplastin time and a thrombin clotting time are commonly available 1.

Factor Xa Inhibitors: Oral factor Xa inhibitors are relatively new on the market thus there is less clinical information available for these agents. The most commonly utilized oral medications from this class are apixaban and rivaroxaban. Factor Xa inhibitors are less dependent on renal clearance and have similar half-lives as dabigatran (see Table 1). They act by binding directly to free factor Xa, complexed factor Xa, or Xa that is part of an active blood clot 5. The recommendations for perioperative management of factor Xa inhibitors differ slightly from those of DTIs (please see Table 1)1. Perioperative testing for residual anticoagulant effects are best assessed by an anti-factor Xa assay.

MANAGEMENT OF ANTICOAGULATION FOR ELECTIVE PROCEDURES

The determination of periprocedural bleeding risk requires an assessment of patient related risk

(ie prior VTE, cancer) and type of procedure (ie superficial lipoma resection versus exploratory laparotomy) as well as the class of anticoagulants the patient is using8. When assessing risk of continuation or discontinuation of anticoagulant medications for elective procedures, the anesthesia provider must carefully balance the risks of thrombus formation against the risk of bridging therapy. Details regarding assessment of patient and procedural risks are addressed in the American college of Chest Physicians supplement entitled “Perioperative Management of Antithrombotic Therapy” 9. In general, anticoagulants are continued with low risk procedures and discontinued (with or without bridging) for high risk procedures8, 9. The choice of bridging agent differs based upon anticoagulant in use, type of procedure, provider preference as well as patient’s renal function8, 9. It is also noteworthy that the use of bridging agents in high risk patients remains controversial, supported only by two randomized controlled trials in the perioperative literature8. Furthermore, there is no consensus with regards to management of moderate risk patients therefore decisions made about anticoagulant continuation, discontinuation, or bridging should be made only after careful consideration of patient and surgical factors9.

Risk stratification of patients with atrial fibrillation, mechanical valves or prior history of venous thromboembolism is dependent upon the CHADS2 score, position and type of valve and time interval between VTE event and surgery respectively9. There is literary support of discontinuation of warfarin in patients at high risk of bleeding approximately five days prior to the procedure 8, 9. Bridging occurs with administration of LMWH or a heparin infusion which is then discontinued within 12- 24 hours of the procedure. Once hemostasis is achieved post operatively, warfarin is re-initiated (usually within 24 hours) and the international normalized ratio (INR) monitored until it is in the therapeutic range prior to discontinuing bridging therapy9. Patients bridging with a heparin infusion should continue the medication until four to six hours prior to the procedure. A PTT is not required but is sometimes drawn in patients with impaired renal function to ensure adequate clearance of the medication prior to incision, especially with procedures such as craniotomy where bleeding into a small space can have catastrophic effects. Similar to warfarin, heparin may be restarted post operatively once adequate hemostasis is confirmed.

MANAGEMENT OF ACUTE BLEEDING

It is well established that patients who present for elective or emergency surgery while continuing their anticoagulant medications are at increased risk of bleeding and intraoperative need for blood transfusion. No direct reversal agents for the NOCs discussed above is currently available. For mild to moderate bleeding, it is recommended that patients be managed supportively and the NOCs held until the medication is cleared systemically 4. For severe bleeding, treatment is supportive and activated charcoal (if medication was given over preceding two hours) as well as hemodialysis (in the case of impaired renal function) may be considered to reduce absorption and hasten drug excretion 4. Because rivaroxaban is highly protein bound, hemodialysis does not effectively remove it from plasma.

There is no data to support use of fresh frozen plasma (FFP) to aid hemostasis in actively bleeding patients unless a coagulopathy is present. The literature supports critically evaluating the clinical picture and tailoring administration of blood products accordingly (i.e. packed red blood cells for anemia, FFP for coagulopathy, platelets for thrombocytopenia). If bleeding is life threatening, use of general hemostatic agents such as prothrombin complex concentrates (PCC), or anti-inhibitor coagulant complex (aPCC) may be considered (Table 2). Suggested doses are 50U/kg of PCC for rivaroxaban and 80U/kg of aPCC for dabigatran 4, 7. No

randomized control trial at this time supports the clinical efficacy of these agents so additional research in this arena is necessary. There is promising in vitro evidence that activated factor VII may be beneficial in acute bleeding states but to date there are no studies in humans supporting its use. A monoclonal antibody targeted to dabigatran is in development and is projected to enter clinical trials in the near future 7.

ASRA GUIDELINES AS IT RELATES TO NEWER ANTICOAGULANTS
The ASRA guidelines contain no specific recommendations about the DTI and factor Xa inhibitors mentioned above. The authors recommended a “cautious” approach due to lack of information regarding specifics of block performance and anesthetic technique in the studies evaluated 10.

POST OPERATIVE PAIN MANAGEMENT
Given patient age and multiple co-morbid conditions, post-operative pain control that utilizes a multi-modal approach is highly recommended for management in order to minimize side effects while enhancing patient comfort. In light of her recent use of a direct thrombin inhibitor (dabigatran), epidural or spinal analgesia is clearly contraindicated. Intraoperative administration of intravenous acetaminophen should be used to decrease patient’s post-operative opiate needs.

Post-operative pain control may be achieved by use of patient controlled analgesia (PCA) pump containing fentanyl, morphine, or hydromorphone. With a past medical history notable for obesity, and obstructive sleep apnea, fentanyl is the drug of choice due to its relatively short duration of action, high potency and ease of titration. Once the patient is able to take oral medications, adjuvants such as acetaminophen (650mg TID), celecoxib (200mg daily), and oxycodone (sliding scale, titrated to pain score) may be utilized. For this elderly patient, use of bedsideoxygen saturation monitor and end tidal carbon dioxide monitor should be seriously considered.

MANAGEMENT OF ANTICOAGULATION POSTOPERATIVELY
Preoperatively, the patient’s thrombotic risk, procedural related risks, and specific anticoagulant use guides management; however, postoperatively an assessment of procedural bleed risk determines anticoagulation strategy. In the past, data from the RE-LY trial has served as a guideline for development of peri-procedural antithrombotic strategy 3. Two points of concern with regards to restarting NOCs postoperatively are their rapid onset of action (which may cause or worsen post-operative bleeding diathesis) and the potential adverse effect of proton pump inhibitors on drug absorption through the gastrointestinal tract 1. The literature supports reinitiating NOCs only when adequate hemostasis is established, delaying as necessary in patients at high risk of post-operative bleeding. For dabigatran, the evidence suggests that resuming anticoagulation the day after surgery (low bleeding risk surgery) or two to three days post operatively (for high bleeding risk surgery) carries similar risk profile as patients given prophylactic enoxaparin 1, 3. Rivaroxaban may be initiated on post op day one (or at least 24 hours after surgery) for low bleeding risk surgery and on post op day two or three for higher risk procedures 1. In patients who are nil per os, enoxaparin may be used to bridge until oral intake is safe.

CONCLUSION
The management of anticoagulants in the perioperative period is complex. While the

pharmacodynamics and pharmacokinetics of older anticoagulation agents are well established, the 'rules' regarding the NOCs are still in question. When determining whether to continue or stop anticoagulation pre operatively or to bridge with medications from a different class, multiple patient and surgical factors must be carefully balanced to minimize the risk of adverse perioperative outcomes (especially bleeding or new VTE formation) to the patient. As more information about these NOCs becomes available, including the development of possible reversal agents, we will be better able to develop guidelines that aid practitioners in the management of this very complex patient population.

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