Lesson S08: PreAnesthetic Assessment of the Patient on Low Dose Aspirin and a Thienopyridine – Part 2

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Needs assessment

Combination therapy with low dose aspirin and a thienopyridine, such as clopidogrel (Plavix®), is commonly prescribed for patients with risk factors for myocardial infarction, cerebrovascular accident and embolic phenomenon. Because of the widespread use, physicians are more frequently confronted with patients who require surgery while receiving dual antiplatelet therapy. Concerns include excessive bleeding in patients requiring emergent surgical care, or the development of hematoma in patients receiving regional block. Fatal myocardial infarction has recently been described following the discontinuation of clopidogrel in patients with drug eluting stents (i.e. stents coated with medication that is slowly released to prevent the growth of scar tissue in the artery lining). Physicians should be knowledgeable of the medical evidence so that they may properly advise surgical candidates receiving antiplatelet medications as to the risks and timing of surgery and the impact of anesthetic techniques.

Objectives

At the end of the lesson, the participant will be able to:

1. Describe a preoperative workup for a patient with suspected coagulopathy.
2. Note the specific laboratory testing for patient with coagulopathy.
3. Discuss drug interactions with herbal preparations.
4. List findings of a physical exam that are indicative of potential problems.
5. Evaluate the limitations of test for bleeding time.
6. Explain preoperative considerations for patients on low dose aspirin.
7. Understand the recommendations for patients who have had a drug eluting stent placed.
8. Draw up an anesthetic plan for a patient on dual antiplatelet therapy.
9. Discuss considerations for discontinuing anticoagulant therapy preoperatively.
10. Understand the perioperative complications that may occur in a patient on aspirin therapy.

**Case Presentation**

A 73 year old woman with a long standing history of osteoporosis was examined in the holding area of the operating room. A total knee replacement was scheduled that day. She had a past history of hypertension and coronary artery disease. She was morbidly obese and wore a Med Alert® bracelet indicating that she had a difficult airway. A note from her cardiologist reported that she had a drug eluting stent placed 3 months prior and she had been advised to take clopidogrel 75mg and aspirin 81mg daily. She stated that she stopped the clopidogrel for the past 5 days as recommended by her orthopedist.

**Preoperative Assessment**

The preanesthetic assessment of the patient for neuraxial block is substantially similar for patients undergoing general anesthesia, with some additional considerations. Communication with the surgeon is crucial when choosing a regional technique for a patient who is maintained on antiplatelet therapy. Prior to the procedure, the anesthesiologist should be informed of the anticipated length of a procedure; the patient position on the table during the procedure; anticipated blood loss; the required degree of muscle relaxation; and technical details such as potential impairment of hemostasis (e.g., prostatectomy) or whether the patient requires heparinization or other thrombolytic therapy (e.g., vascular surgery).

The following specific areas should be pursued when performing a preoperative assessment.

**Patient History**

A medical history should identify diseases or medical conditions for which low dose aspirin reduces morbidity and mortality. The consequences of withholding aspirin for a prolonged period (e.g., a potential increase in the risk of disease expression) should be evaluated.10

Many groups of patients routinely use medications which affect coagulation. Orthopedic patients undergoing major joint surgery often have chronic inflammatory diseases, such as rheumatoid arthritis, treated with non-steroidal anti-inflammatory drugs including aspirin, naproxen, ibuprofen, and ketorolac. Pregnant patients with systemic lupus erythematosus, thrombotic purpura, and antiphospholipid antibodies syndrome, are frequently prescribed low dose aspirin (50 to 150 mg per day) to improve pregnancy outcome.24,40,41,42 Low-dose aspirin has also been advocated as a prophylactic and a therapeutic agent for pregnant women with preeclampsia. Several studies show that low-dose aspirin reduces the incidence of preeclampsia, thus decreasing risk for uteroplacental or umbilical placental vascular insufficiency and thrombosis.41 There is also considerable evidence supporting use of low dose aspirin in many individuals at risk of cerebrovascular disease, stroke or myocardial infarction.43
The medical history should include an assessment of:

- bleeding tendencies including bleeding during prior surgical or dental procedures, epistaxis, menorrhagia, easy bruising, and/or bleeding abnormalities in other family members.

- previous back injury or surgery as this may increase the difficulty of needle insertion. Laminectomy or scarring from earlier procedures may make identification of landmarks difficult.

- neurological diseases. Patients with signs and symptoms of neurological disease may not be candidates for regional techniques as there may be medicolegal considerations in addition to medical contraindications.

- prior surgical procedures and anesthesia with associated complications, especially those events that relate to difficult intubation or complicated neuraxial block. Regional techniques are often a better option for a patient with anatomical difficulty or oral anomalies that create a “difficult airway,” whenever surgery allows.

**Medications**

Patient medications should be recorded with special attention to those that are known to influence the process of hemostasis (gold, thiazide diuretics, quinidine, sulfanilamides, aspirin, acetaminophen, phenytoin, digoxin, alpha methyl dopa, clopidogrel, and warfarin). It is important to ask the patient about their use of herbal preparations since some of these compounds may inhibit coagulation. Many patients regard herbal preparations as “safe” and are not inclined to report them to a physician. A spontaneous spinal/epidural hematoma was reported in an 87 year-old male with platelet dysfunction related to excessive garlic ingestion. Garlic-induced decreased platelet aggregation has also been described. Garlic may augment the effects of warfarin, heparin, non-steroidal anti-inflammatory agents (NSAID’s), aspirin and may result in an abnormal bleeding time, which can theoretically lead to an increased risk of intraoperative or postoperative bleeding. Awareness of this action is especially important for patients in pain management settings who may present for neuraxial block. Ginger has been found to be a potent inhibitor of thromboxane synthetase enzyme, which can prolong bleeding time. The root may also be used as seasoning and as a taste enhancer with other less palatable herbs. Use of ginger may increase bleeding time; therefore, its use should be avoided in patients on anticoagulants like warfarin and heparin or drugs such as NSAIDs and aspirin. Gingko biloba is used as an antioxidant, circulatory stimulant, and for the treatment of intermittent claudication, tinnitus, vertigo, memory enhancement, and sexual dysfunction. A large placebo-controlled, double-blind, randomized trial of EGB761 studied the effectiveness in patients with dementia and concluded that gingko extract was capable of stabilizing and modestly improving cognitive performance and social functioning ability. Further, gingko biloba has been shown to have potential for improvement of symptoms of intermittent claudication. Study subjects using gingko biloba experienced reduction in pain in their lower extremities with an improved claudication distance. The herb has the potential to inhibit platelet-activating factor, modulate nitric oxide, and possesses an anti-inflammatory effect. Gingko biloba is considered to be relatively safe with few side effects, limited to mild
gastrointestinal upset and headache. However, a few disturbing case reports have been published. Gingko biloba-induced spontaneous hyphema (bleeding from the iris in the anterior chamber of the eye), subarachnoid hemorrhage, and spontaneous bilateral subdural hematomas have been described. Of additional concern is the gingko toxin in both the gingko leaf and seed, which is thought to be neurotoxic.

Although there have been no placebo-controlled double-blind studies regarding potential gingko-induced abnormal bleeding, concomitant use with aspirin, or any NSAIDs and anticoagulants such as warfarin and heparin, is not recommended as gingko may increase the potential to bleed in these patients.

Clopidogrel

Antithrombotic therapy frequently consists of clopidogrel combined with aspirin. In the “Clopidogrel in Unstable Angina to prevent Recurrent Ischemic Events” (CURE) trial, 12,562 patients were randomly assigned to one of two groups – (1) those receiving clopidogrel and aspirin; (2) those receiving placebo and aspirin. Patients either underwent cardiac surgery, percutaneous coronary intervention or medical therapy. The study found that there was a significant reduction in cardiovascular death, myocardial infarction or stroke for the patients assigned to the clopidogrel/aspirin group. The combination therapy increased the risk of major bleeding by 1% but there was no significant increase in life threatening bleeding. The drugs were not discontinued preoperatively. Researchers utilized the CURE trial data and patient base to determine the benefits of adding different doses of aspirin to clopidogrel. The results showed that the combination therapy was beneficial in patients with acute coronary syndrome, regardless of the aspirin dose. Bleeding increases with aspirin dose, with or without increase in efficacy. The optimal aspirin dose appeared to be between 75-100mg daily.

Physical Examination

A pre-procedure physical exam should be performed and documented. The following points should be considered:

- An assessment of the back should be performed for identification of landmarks, anatomic abnormalities and possible infections at the site of needle placement.
- A neurological examination should identify and evaluate deficits.
- Physical findings as enlarged spleen or liver, ascites, unexplained lymphadenopathy, or joint deformities should be considered for potential underlying diseases that can impact outcome.
- Skin lesions such as petechiae, ecchymoses, telangiectasia (Osler Weber Rendu disease), brown skin pigmentation (hemochromatosis); stigmata for liver failure, such as spider angiomas, palmar erythema or jaundice should be noted.
Laboratory Tests

If screening for bleeding history is negative and the patient is not receiving any anticoagulant therapy, only PTT, PT, and a platelet count are recommended. If screening for bleeding history reveals a suspicious hemostatic abnormality, a full evaluation of the following may be indicated:

- adequacy of formation of hemostatic plugs: platelet count plus a bleeding time.
- adequacy of the blood coagulation reactions: PTT and PT.
- size and stability of the fibrin clot.

If these tests are negative, then the following additional tests may be considered:

- Qualitative platelet assessment: repeated bleeding time after 600 mg of aspirin (von Willebrand’s disease), platelet aggregation tests, and a Ristocetin cofactor assay.
- Measuring factor VII and factor IX coagulant activity (to exclude hemophilia).
- Performing a thrombin time utilizing a thrombin concentration that gives a time of 15-20 sec with normal plasma. This test may reveal patients with dysfibrinogenemia or a weak heparin-like anticoagulant not detected by PT or PTT.

If these additional tests are normal, further investigational testing can include measuring the level of alpha 2-antiplasmin activity.

A comprehensive battery of testing for suspected coagulopathy is of particular importance to the surgical procedure because it is usually possible to choose an alternative anesthetic technique to a neuraxial block. Nevertheless, laboratory evaluation of patients on low-dose aspirin remains a topic of some controversy perhaps more for legal reasons than because of the medical evidence presented. MacDonald recommends assessment of platelet function in all aspirin treated patients who are undergoing extradural anesthesia. Measurement of the bleeding time is a practical but unreliable test of in vivo platelet function. Duke introduced this test to medical practice in 1910. Since then, it has undergone many modification such as the Ivy technique (uses blood from skin, with a normal bleeding time of 2-7 minutes), and the modified Ivy technique using a Surgicutt device or a Simplate (normal, 2.75 - 8 minutes). The goal of all of these modifications is to achieve reproducible results where the depth and direction of incision, venostasis, and cuff pressure, etc. should be standardized. The upper limit of normal bleeding time is set at 10 min for a standard technique test. Bleeding times measure the time required for bleeding to stop from a shallow incision made under standardized conditions. It indicates the functionality of the platelet and vascular components of coagulation and is normal in the presence of coagulation factor deficiencies. Bleeding time is prolonged when platelets are less than 60,000 per liter or when there is a functional abnormality. Increased bleeding time correlates to susceptibility to bleeding. Sonksen et al. recommend 48 h as the optimum time to withhold aspirin before central nerve block according to the measurement of bleeding time in healthy volunteers. However, as noted, many authors believe that post-aspirin bleeding time is an unreliable predictor of intraoperative hemostasis. It can be greatly affected by the technique used during the test. Bleeding time is not always a reliable indicator of platelet function. Although the bleeding time can be normal after 2-3 days of discontinuing aspirin therapy, platelet function may still be abnormal for 7-10 days. Furthermore, in many patients who take aspirin, the bleeding time may be normal, and in contrast, an abnormal bleeding time does not always indicate ineffective hemostasis during surgical procedure.
Sibai et al. found no increase in the maternal blood loss during delivery and postpartum in spite of an increased bleed time.24 According to the study by Horlocker et al., there was no difference in preoperative platelet counts, PTs, aPTTs, or bleeding times between patients with and without minor hemorrhagic complications.23

Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy may also be made by thromboelastography platelet mapping (TEG-PM). Statistically significant platelet inhibition after antiplatelet therapy can be identified.61 Other authors have concluded that TEG may be of no help in assessing the degree of anticoagulation but effects of platelet transfusion may be reflected by adenosine diphosphate and epinephrine aggregometry.62

**Stent Placement**

Coronary stenting has an increasing role in multivessel and left main CAD.63 Management of patients with stents is an important patient safety issue as perioperative thrombosis is a life threatening complication for patients with either a bare metal or (more importantly) drug eluting stent. Noncardiac surgery appears to increase the risk of stent thrombosis and myocardial infarction especially early after placement. The incidence of complications is increased when dual antiplatelet therapy is discontinued preoperatively.64 The risk of myocardial infarction when clopidogrel is stopped prior to surgery is 20% when alternative antithrombotic prophylaxis is not used.65 The American Society of Anesthesiologists has issued a practice alert for perioperative management of patients with coronary artery stents, emphasizing that premature discontinuation of dual antiplatelet therapy in patients with new stents is associated with increased risk of life threatening stent thrombosis.66 The time period is 4-6 weeks for bare metal stents and 21 months for drug eluting stents.

**Anesthetic Plan and Postoperative Complications**

Antiplatelet drugs, by themselves, may not increase the risk for the development of spinal hematoma in patients having epidural or spinal anesthesia, according to current studies.62 Several societies have produced guidelines.67,68 If possible, aspirin or clopidogrel should be withheld for 7-10 days before neuraxial block. Therapy with glycoprotein-11b/111a-receptor antagonists is a contraindication for neuraxial block. Coumadin derivatives should be withdrawn and replaced with a different form of anticoagulation. The use of low molecular weight heparin in prophylactic dosage is not a contraindication for neuraxial block. However, even with adherence to these guidelines, epidural hematoma after neuraxial anesthesia has been reported.69 Other literature reviews have concluded that for patients undergoing cardiovascular surgery, aspirin should be maintained and clopidogrel stopped.70 A national database audit of 55,567 patients undergoing cataract surgery while on anticoagulant medication concluded that addition of clopidogrel increased minor complications of sharp needle and subtenon’s cannula local anesthesia by 8%.71 There was no increase in hemorrhagic complications causing a negative outcome on sight.

There is no reliable test, including bleeding time, to guide antiplatelet therapy. Careful preoperative assessment of patients should be done to reveal any impairment of hemostasis.21 The decision to perform a neuraxial block on a patient receiving low-dose aspirin should be made on an individual patient basis.14 The surgeon and the anesthesiologist performing the central block should consider: (1) the risk of spinal hematoma; (2) the benefits of regional anesthesia for the specific patient; and (3) the risk of stopping antiplatelet therapy for patients prone to thromboembolism. Horlocker et al. and
Vandermeulen et al. found that large bore needles, regional anesthetic techniques (continuous spinal > continuous epidural > single-dose spinal), and difficult needle placement with multiple passes were all significant risk factors for hemorrhagic complications. The same authors did not find any difference in the incidence of minor hemorrhagic complications between midline or paramedian approaches. Romer et al. summarized cases with thoracic epidural and did not regard aspirin therapy as an absolute contraindication to epidural insertion. They recommended withholding low dose aspirin therapy before neuraxial block only for patients with abnormal clotting studies. The risk of stopping aspirin therapy for a week versus the risk of myocardial infarction or stroke is not known. The American Society of Anesthesiologists has also updated the Practice Guidelines on Transfusion Therapy and recommends that anticoagulants be discontinued for a sufficient time preoperatively to allow the anticoagulant effect to dissipate preoperatively, noting that the effects of clopidogrel may last for 7 days or more.

Spinal epidural hematomas occur more often than subarachnoid hematomas because of prominent epidural venous plexi. Subarachnoid bleeding is often not clinically significant because of dilution and redistribution. The source of subarachnoid bleeding may be the result of damaged radicular vessels.

Patients who present for day care surgery should be evaluated individually. Often aspirin and clopidogrel can be continued but high risk patients for high risk surgery should not be managed on an outpatient basis or in an office setting.

Patients receiving neuraxial block should always be monitored for potential development of spinal hematoma. All patients must be closely monitored for neurological complications, especially patients with a greater risk of neuraxial bleeding (e.g., older women, patients with osteoporosis, and those that required multiple attempts at needle placement). Symptoms of impending complications include new onset of weakness or numbness. A continuous catheter technique may mask symptoms of spinal hematoma formation. Therefore, the block should be allowed to wear off at regular intervals so that neurological status can be properly evaluated. The only treatment of spinal hematoma is emergency decompressive laminectomy with the evacuation of the spinal hematoma. Complete recovery of neurological symptoms is likely if decompression is performed within 29 hours. In patients in whom decompression was delayed for 66 hours, recovery was partial.

Management of the Case Presented

The patient was instructed that regional anesthesia is typically indicated in circumstances where the patient has a difficult airway. However, given the anticoagulant status of the patient, general anesthesia was presented as a reasonable alternative especially since equipment such as the Glidescope®, or an intubating supraglottic airway, are readily available. The patient was informed of the risk of myocardial infarction due to discontinuation of clopidogrel within a year of a drug eluting stent placement. The surgeon was included in all conversations. The risks of surgery as opposed to a delay for this elective procedure were discussed. After review of the data, the decision was made to postpone the surgery for 1 month. During that time, clopidogrel and aspirin would be continued but herbal preparations and nonsteroidal medications would be withheld. Pain would be treated with a narcotic patch as advised by her pain specialist. Examination of her back suggested that placement of a regional anesthetic would be challenging. She was told that ultrasound technology could be used to increase the success rate. Her previous anesthetic records were reviewed and indicated that the difficulty in endotracheal tube placement may have been related to lack of the equipment available on
a difficult airway cart. Together with her operative team, she felt that she would prefer general anesthesia when she returned at a later date.

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1. To predict hemorrhagic complication with high accuracy in patients receiving low-dose aspirin, the most reliable test is:
   a. PT and/or PTT
   b. Bleeding time
   c. Platelet count
   d. No tests are completely reliable

2. Which of the following statements is most accurate?
   a. Spinal epidural hematomas occur more frequently than clots in the subarachniod space.
   b. Subarachnoid bleeding has more devastating neurologic effects than epidural bleeding.
   c. The source of an epidural hematoma is radicular vessels.
   d. All of the above are accurate statements.

3. Spinal hematoma:
   a. can have symptoms that are masked by continuous catheter technique.
   b. can resolve spontaneously.
   c. should be operated only if conservative treatment fails after 24 hours.
   d. should be suspected only if weakness or numbness remains 2 days after spinal or epidural anesthesia has been terminated.

4. Which of the following statement is FALSE regarding herbal preparations?
   a. Herbal preparations are safe to use with anticoagulants.
   b. A medication history should include use of herbal therapies.
   c. Patients on aspirin therapy should not consume Gingko biloba.
   d. Garlic may augment the effects of warfarin.

5. Bleeding time:
   a. returns to normal range in 48 - 72 hours after discontinuation of aspirin therapy
   b. is practical but unreliable
   c. has been questioned as a reliable indicator of platelet function
   d. all of the above
6. **Data from the CURE trial demonstrated:**
   a. efficacy increases with aspirin dose
   b. combination therapy (clopidogrel/aspirin) increased the risk of life-threatening bleeding
   c. bleeding increases with aspirin dose without an increase in efficacy
   d. none of the above

7. **What are the recommendations regarding anticoagulation and coronary stents?**
   a. No matter what type of stent has been placed, all anticoagulant medication should be discontinued before neuraxial anesthesia.
   b. After drug eluting stent placement, clopidogrel should not be discontinued.
   c. Bare metal and drug eluting stents are essentially identical and do not require anticoagulant medication.
   d. The risk of myocardial infarction if clopidogrel is stopped before surgery in a patient with a drug eluting stent is 50%.

8. **Which factors increase the risk of epidural hematoma formation postoperatively?**
   a. Older women
   b. Multiple attempts at placement of the block
   c. Osteoporosis
   d. All of the above

9. **Initial recommended laboratory tests in screening for a suspected coagulopathy include:**
   a. no history of bleeding is sufficient
   b. PTT, PT and platelet count
   c. Measurement of all specific factors
   d. Alpha 1-antiplasmin activity

10. **An abnormal bleeding time:**
    a. means nothing
    b. does not always indicate ineffective hemostasis
    c. is always a reliable indicator of platelet function
    d. usually persists for 2 weeks after discontinuing aspirin therapy