Lesson S07: PreAnesthetic Assessment of the Patient on Low Dose Aspirin and a Thienopyridine – Part 1

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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 the role of platelets in coagulation.
2. Note the effects of aspirin on platelets.
3. Understand the site of action of clopidogrel on platelets.
4. Cite a safe time between discontinuation of dual antiplatelet therapy and administration of neuraxial block for surgery.
5. List the benefits of low dose aspirin therapy.
6. Describe lab tests used to assess bleeding and platelet function.
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. List the indications for aspirin therapy.
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.

**Introduction**

Many studies have shown that small amounts of aspirin (81mg) taken daily can significantly reduce the risk of stroke and myocardial infarction in those at risk for these fatal disease processes. Aspirin acts by decreasing coagulability and may place the surgical patient at risk for excessive or uncontrollable bleeding and gastrointestinal hemorrhage. Furthermore, in cases where spinal or epidural techniques are the anesthetic of choice, neuraxial hematomas can develop and cause paralysis. While much has been written on the topic, patients may still not be adequately informed as to the true risk-benefit ratio of aspirin ingestion.

**History**

On June 2, 1763, the Reverend Edmond Stone of Chipping Norton in Oxfordshire sent a communication to the Royal Society which read as follows:¹

"Among the many useful discoveries which this age has made, there are few which better deserve the attention of the public than what I am going to lay before your Lordship. There is a bark of an English tree, which I have found by experience to be a powerful astringent and very efficacious in curing agues and intermittent disorders."

Reverend Stone described the bark of the willow (Salix alba) which contains salicin, the glycoside of salicylic acid. In his quest to find a substitute for the expensive, imported cinchona (quinine) bark from Peru, Stone discovered that salicylates reduce the fever and aches associated with prevalent illnesses. Stone’s research was based in part on a commonly held belief that effective treatments from nature are likely to be found in proximity to the area with the highest incidence of the specific disease. Rheumatism and arthritis were prevalent in the cold, damp regions of England where the willow commonly flourished. Stone reported improvement in a study group of 50 patients with "ague" (i.e. fever, shivering) to whom he administered a powder of 20 grains of willow bark in water every 4
hours. The medical value of the willow was also described by many of the early Greek scholars and physicians including Hypocrates (4th century BC) who advocated the chewing of willow leaves for relief of labor pains. Pliny (1st century AD), Galen (2nd century AD), and Paulus of Aegina (6th century AD) also referred to the analgesic properties of willow. Celsius wrote about several species of the Salix - S. alba, fragilis and purpura. Dioscorides recommended that the bark and juice of the willow be used for hemoptysis, arthritic complaints or externally for the removal of calluses and corns. Aretius (2nd century AD) and the early Arabians also described similar uses for the bark.

Salicin was first extracted from willow bark in 1827. By 1833, Merck, a pharmacist, obtained a clean preparation of willow bark. Salicylic acid was prepared from saligenin (obtained from hydrolysis of salicin) in 1838. It was synthesized from phenol in 1860 by Kolbe and his students at Marburg.

Acetylsalicylic acid or aspirin, a synthetic derivative of salicylic acid, was prepared by Felix Hoffman, a German chemist, in the Bayer Company, in 1893. Six years later acetylsalicylic acid was introduced to medical practice by Dresser. Acetylsalicylic acid was used mainly as an antipyretic, anti-inflammatory and analgesic drug until the 1970’s. In 1968, the antiplatelet activity of aspirin was discovered and it became widely prescribed as an antithrombotic medication.

**Primary Hemostasis and Aspirin**

The process of hemostasis is a coordinated interaction with three major components:
1) vasoconstriction of damaged vessels at the site of injury;
2) formation of a platelet plug;
3) activation of the coagulation cascade resulting in fibrin clot formation.

Trauma to blood vessels causes reflex vasoconstriction which creates a plug at the site of vessel damage. Platelets bind to von Willebrand factor as blood is exposed to subendothelial structures. Continued activation of platelets leads to the formation of a larger hemostatic plug. “Primary hemostasis” is defined by reflex vasoconstriction and the formation of a platelet plug which are essential to the cessation of bleeding at any area of minor trauma such as the insertion site of a blood vessel during epidural needle placement.

The intrinsic and extrinsic pathways of the coagulation cascade are activated by the release of tissue factors from the injured site into the blood or from exposure of the blood to collagen. Fibrin strands develop to reinforce the platelet plug. The failure of any component in the pathway can lead to coagulation defects and bleeding.

At the site of vessel injury, the presence of collagen activates the surface receptors of platelets triggering the release of granules containing factors such as serotonin, ADP, catecholamines, and other nucleotides. This process is known as the “platelet release reaction”. Inside the cell membrane, phospholipase releases arachidonic acid. Cyclooxygenase converts arachidonic acid to prostaglandin intermediates and thromboxanes. Thromboxane A2 produces vasoconstriction and induces irreversible platelet aggregation. Healthy and intact endothelium can synthesize prostaglandins to produce prostacyclin which causes vasodilatation and inhibition of aggregation. The balance of the relationship between levels of prostacyclin and thromboxane A2 determines whether platelets aggregate or circulate freely (Figure 1)
Aspirin produces irreversible acetylation of cyclooxygenase, a key enzyme in the synthesis of prostaglandins. Platelet cyclooxygenase is inhibited by low dose aspirin (30-300 mg daily). Inhibition of the prostacyclin production in intact vascular endothelium requires higher doses (1-2 g daily). Platelets are incapable of producing new cyclooxygenase and therefore, the aspirin effect lasts the lifetime of the platelets. Cyclooxygenase (COX) exists in two isoforms: COX-1 and COX-2. COX-1 can be found in most cells and tissues. It is involved in many functions, such as autoregulation of blood flow, and control of homeostasis by modulation of platelet function. COX-2 (mRNA and protein forms) is normally undetectable in tissues, but can be rapidly induced by factors, such as cytokines, endotoxin, growth factors, inflammation, and mitogens. Aspirin inhibits COX-1 more actively than COX-2. It is about 170 times less effective in the inhibition of COX-2. Therefore, the presence of even a low amount of COX-2 in the platelets may decrease the efficacy of aspirin. There may be a decreased expression of COX-2 in some healthy individuals (“hyper-responders”) which causes a more prolonged bleeding time than occurs in the population at large.

Thienopyridine derivatives, such as prasugrel, ticlopidine and clopidogrel, are ADP receptor/P2Y12 inhibitors. Clopidogrel is the most commonly prescribed thienopyridine in the United States. This group of drugs inhibits platelet aggregation by preventing the binding of ADP to the receptor and blocking the ADP-mediated activation of the glycoprotein GP 11b/111a complex. The drug also acts by inhibiting the amplification of platelet activation by released ADP. The action is irreversible and exposed platelets are affected for their lifespan. Dose dependent inhibition of platelet aggregation
occurs 2 hours after a single oral dose of clopidogrel (75mg), and with continued daily dosing, steady state (40-60% inhibition) is reached by day 3-7. Platelet aggregation and bleeding time gradually return to normal in about 7-10 days after discontinuation of therapy although there is considerable patient variability. Aspirin has not been shown to modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of up to 500mg aspirin twice a day did not significantly increase the prolongation of bleeding time induced by clopidogrel. However, clopidogrel potentiates the effect of aspirin on collagen-induced platelet aggregation. The 2 drugs are frequently administered together for long periods of time. There is good evidence to support the combination of aspirin and clopidogrel for patients with acute coronary syndrome and those with percutaneous coronary intervention, but no evidence to indicate a beneficial effect in primary prevention of coronary artery disease (CAD), atherosclerotic ischemic events, secondary prevention of stable CAD or prevention of cardioembolic stroke in patients with atrial fibrillation. Increased surgical and traumatic bleeding may occur.

Neuraxial Anesthesia

About the same time that aspirin was introduced to general medical practice, spinal anesthesia was described. J. Leonard Corning wrote about the injection of 2% solution of cocaine into the space between the interspinous processes of the 11th and 12th dorsal vertebrae in a dog and in a man. It is uncertain whether he achieved epidural or subarachnoid anesthesia. Nevertheless, the method was not widely accepted as a means of inducing surgical anesthesia. The technique of Corning was perfected and introduced into anesthetic practice by August Bier in 1899. The latter also observed that headache, probably due to cerebrospinal fluid leak, could be a severe complication. In 1909, Professor Jonnesco presented a review of 398 operations performed by means of general spinal analgesia using strychnine and stovaine or novocaine following puncture of the arachnoid at all levels. He noted that "fear of pricking the cord (is) unfounded; even if it happens, it is not harmful." He claimed analgesic effect for "one and a half to two hours, a period longer than is necessary to perform any operation." He concluded that "general spinal anesthesia is absolutely safe; it has never caused death nor produced any important complications, early or late....general spinal analgesia will be the analgesia method of the future." One year after Jonnesco’s report of safety, the first spinal hematoma after neuraxial block was recorded.

Risk Factors for Neuraxial Hematoma Formation

Although uncommon, spinal or epidural anesthesia can be seriously complicated by bleeding inside the spinal canal. According to a literature search performed by Vandermulen et al., only 61 cases of spinal hematoma after neuraxial block were reported between 1906 to 1994. This low number of reported complications may be due to fear of legal retaliation. Tryba analyzed the outcomes of more than 850,000 patients who received epidural blocks and 650,000 patients who received subarachnoidal blocks. Statistical analysis showed that the estimated risk for development of a spinal hematoma was 1:150,000 after epidural anesthesia and 1:220,000 after spinal anesthesia for patients with normal coagulation. Cross-checking more than 1,300,000 cases of epidural blocks, Wulf, et al found seven cases of spinal epidural hematoma formation, suggesting an incidence of approximately 1 hematoma in 190,000 epidural blocks. Tyagi identified 60 patients by literature search over a 5 year period that developed spinal hematomas, either spontaneously or after central neuraxial blockade. Twenty patients had undergone neuraxial block and of these, 11 were receiving concomitant anticoagulation. Awad et al analyzed the records of 14,932 patients undergoing
spinal surgery and found 32 (0.2%) who required a second spinal operation within 1 week. While the preoperative use of non-steroidal analgesic agents was identified as a risk, well controlled postoperative anticoagulation was not. It is unclear from this study how many patients received neuraxial anesthesia. Yoon, from a database of 3,720 cases of spine surgery, identified a similar postoperative incidence of epidural hematoma of 0.24% (9 patients). Coagulopathy from medical illness or anticoagulation therapy occurred in 4 cases. Although these data show that spinal hematoma is a rare event, the true incidence of neurological dysfunction resulting from hemorrhagic complication is unknown. Such a determination would require a prospective and randomized study of more than 100,000 patients.

Many retrospective and prospective studies have attempted to identify risk factors which predispose patients to formation of neuraxial hematoma. Coagulopathy and therapeutic anticoagulation are well described risk factors but, as indicated by the aforementioned studies, may not be contraindications for neuraxial block. Advanced patient age and anatomical abnormalities of the back are not risk factors, but these conditions can cause difficult needle placement requiring multiple punctures thereby increasing the risk of hematoma. Difficult or traumatic neuraxial punctures are recognized as major factors for hemorrhage or spinal hematoma formation. Data have demonstrated the association of minor hemorrhagic events (bloody taps) with difficult needle placement. Surgery on the hip and moderate or difficult needle placement increased the incidence of minor hemorrhagic complications from 4% to 60%. Longer duration of surgery and Rh-positive blood type have also been identified as risk factors.

Studies assessing the risk of vessel puncture after epidural anesthesia report a bloody tap incidence from 1% to 10% in non-pregnant patients, and as high as 18% in pregnant patients. One study reported that blood was found in the spinal or epidural needle or catheter in 22% of patients. These studies demonstrate that the risk of vessel damage after spinal or epidural needle placement is high.

Aspirin therapy can increase the amount of bleeding and therefore lead to the development of a spinal or epidural hematoma. The rarity of spinal or epidural hematomas precludes randomized trials. Most of the evidence is derived from retrospective studies or prospective descriptive studies. In the retrospective survey by Vandermeulen et al., only 1 in 61 spinal hematomas was related to aspirin therapy alone. Since the time that this data was reported, the use of daily aspirin has greatly increased particularly among older people who constitute a group that is likely to be better managed by neuraxial techniques. Sibai et al. conducted a double blind, placebo-controlled study with 3135 nulliparous women to assess the effect of low-dose aspirin. Among the 851 women who received epidural anesthesia for labor and delivery, 451 received low-dose aspirin and 440 received the placebo. In spite of an increased bleeding time in women receiving low-dose aspirin there were no adverse effects related to epidural anesthesia.

The Collaborative Low-Dose Aspirin in Pregnancy (CLASP) study analyzed 2783 cases of epidural anesthesia with 1422 patients receiving aspirin and 1361 patients receiving placebo. In this study, three cases had a bloody tap - one in the aspirin group and two in the placebo group – and no cases of epidural hematoma formation. The reported 0.1% incidence of bloody tap is much lower than earlier reported rates. The absence of hematoma formation is consistent with earlier findings of Horlocker et al., showing no correlation between antiplatelet therapy and bloody needle or catheter placement.
**Aspirin and Neuraxial Block**

Aspirin causes irreversible inhibition of COX-1 and 1lifelong platelet dysfunction. The level of serum thromboxane B2 (a metabolite of thromboxane A2) has been used as an indicator of platelet function in an *in vitro* aggregation study. The mean platelet life span is approximately 10 days. Therefore, 5 to 6 days after the last aspirin dose, approximately 50% of circulating platelets should have regained normal function. Based on this principle, aspirin therapy should be withheld up to 7-10 days before neuraxial block.\(^4\)\(^,\)\(^15\) Sonksen et al. proposed that the optimum time for withholding aspirin before central nerve block or other invasive procedures is 48 hours.\(^10\) The authors conducted a randomized, double-blind, placebo-controlled study to determine changes in primary hemostasis 48 hours after discontinuation of aspirin therapy. Bleeding time was used to determine functional return of primary hemostasis. Other studies have indicated that the value of bleeding time in evaluating platelet function is questionable.\(^26\)\(^,\)\(^27\) Although bleeding time returns to normal range within 48-72 hours after withholding aspirin therapy, platelet function (as assayed in *in vitro* aggregation studies) may take many days to return to normal.\(^23\)\(^,\)\(^28\) Other potential causes of decreased platelet count and function include herbal interactions, sepsis, fever, and thrombocytopenia related to chemotherapy.

**Aspirin and Perioperative Complications**

Use of aspirin as an antithrombotic agent has increased greatly over the past 30 years. It is now routinely administered to patients with both peripheral and coronary vascular diseases because of its ability to prevent platelet aggregation and thrombotic events. The first stroke prevention trial that showed the efficacy of aspirin was completed in Canada in the 1970’s.\(^29\) The dose was 1300 mg daily. By 1990, trials of the effects of antiplatelet agents in preventing adverse vascular events had been completed in over 70,000 high risk patients.\(^30\) The drug most frequently used was aspirin in doses of 75 to 325 mg/day. No evidence was presented that a higher dose or another agent was more efficacious. Two trials compared aspirin 300 mg versus 1200 mg and 30 mg versus 283 mg.\(^31\)\(^,\)\(^32\) Results were similar but gastrointestinal effects were increased at higher aspirin doses. Specifically looking at patients with cerebrovascular disease, the investigation of the North American Symptomatic Endarterectomy Trial found that the perioperative stroke and death rate were lower in those receiving 650 - 1300 mg of aspirin per day as compared to those receiving 0 - 325 mg/day.\(^33\) A subsequent study of 2804 patients assigned to receive either 650-1300 mg aspirin or 81-325 mg aspirin showed a lower stroke, myocardial infarction and death rate in the group receiving the lower dose.\(^34\)

The Women’s Health Study followed 39,876 female professionals over 10 years.\(^35\) Women were randomized to receive 100mg aspirin or placebo every other day. Aspirin use was associated with no effect on the number of total myocardial infarctions but the incidence of strokes was significantly decreased. Large studies have shown that the benefits of low dose aspirin (75-162mg/day) outweigh the risks of serious bleeding.\(^36\) Data from the Aspirin and Carotid Endarterectomy (ACE) trial, suggest that low dose aspirin is superior to high dose therapy in reducing perioperative stroke and death.\(^37\) However, in a recent survey of German neurosurgeons who perform intracranial and spinal surgery, 77% of respondents felt that patients taking low dose aspirin were at increased risk of bleeding; and 58% reported personal experience with excessive perioperative hemorrhage.\(^38\)\(^,\)\(^39\) Eighty percent had a departmental policy for discontinuation of aspirin preoperatively. Desmopressin was the treatment of choice should bleeding occur.

*Part 2 of this lesson will be available in September, 2009.*
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References

35. Buring JE. Aspirin prevents stroke but not MI in women; Vitamin E has no effect on CV disease or cancer. Cleve Clin J Med. 2006; 73(9): 863-70.


POST-TEST

1. **Aspirin is best described as:**
   a. salicylic acid
   b. a naturally occurring substance
   c. a potent anticoagulant
   d. an old drug for whom new actions have been discovered

2. **Retrospective studies indicate that spinal hematoma:**
   a. is a rare event after neuraxial block
   b. develops more often after spinal anesthesia than epidural
   c. is not associated with preoperative use of non-steroidal analgesic agents
   d. always relates to anticoagulant therapy

3. **All of the following are risk factors for spinal hematoma except:**
   a. difficult and traumatic neuraxial punctures
   b. coagulopathy
   c. therapeutic anticoagulation
   d. advanced age

4. **Initial components of primary hemostasis include:**
   a. the response of damaged vessels at the site of injury by vasoconstriction; formation of a platelet plug
   b. activation of the coagulation cascade; formation of a platelet plug
   c. adherence of platelets in presence of Von Willebrand factor; formation of hemostatic plug
   d. exposure of the blood to collagen; activation of prostaglandin synthesis in platelets

5. **Aspirin produces irreversible acetylation of:**
   a. phospholipase
   b. peroxydase
   c. cyclooxygenase
   d. thromboxane synthetase
6. **All of the following statements are true except:**
   a. mean platelet life span is approximately 10 days
   b. cyclooxygenase exists in two isoforms
   c. function of cyclooxygenase in platelets can be restored
   d. inhibition of synthesis of prostacyclin by aspirin is irreversible

7. **Beneficial anticoagulant effects of aspirin:**
   a. have been know for thousands of years
   b. are unreliable
   c. have only recently been discovered
   d. are likely dose related

8. **Cyclooxygenase:**
   a. exists in 2 isoforms
   b. is found in most cells
   c. modulates platelet function
   d. all of the above

9. **Salicin:**
   a. is an extract of willow bark
   b. was identified by Galen
   c. cannot be hydrolyzed to glucose
   d. was introduced to medical practice by Dresser

10. **Features of platelets include:**
    a. surface receptors are activated by cyclooxygenase
    b. presence of platelet granules containing many biologically active factors
    c. a "non-release" mechanism
    d. similarities to endothelial cells in the ability to produce cyclooxygenase