2017 Oregon Dental Conference®
Course Handout

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Course 8171: “Dental Management of Patients on Antithrombotic Medications”
Saturday, April 8
1 pm - 3 pm
Dental Management of Patients on Antithrombotic Medications

Oregon Society of Periodontists
Oregon Dental Conference
April 8, 2017
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Course Objectives

- Discuss how hemostasis is achieved.
- Define medical conditions for which the physician may prescribe antiplatelet and/or anticoagulation medications.
- Improve your knowledge of antithrombotic medications; including the new drugs.
- Learn techniques to comfortably manage these patients during their dental treatment.

Presentation Overview

- Review phases of hemostasis
- Review clotting cascade
- Antiplatelet medications
  - Aspirin, clopidogrel, and others
- Anticoagulant medications
  - Warfarin
  - Heparins
  - The new oral anticoagulants (four now available)
- Patient management guidelines
- Discuss the limited scientific evidence
Three Phases of Hemostasis

- **Vascular phase** – vasoconstriction slows or stops blood flow (localized response lasts up to 30 minutes)
- **Platelet phase** – damaged endothelial cells release von Willebrand’s Factor which promotes platelet adhesion. Aggregation of platelets leads to a platelet plug and the release of Factor III, activating the extrinsic pathway
- **Coagulation phase** – begins 30 seconds and results in thrombus formation

Fibrinolytic Phase

- Dissolution of the clot once it has served its purpose of hemostasis
- Prevents coagulation of intravascular blood away from site of injury
- This stage relies on plasminogen, a proenzyme for plasmin; plasminogen activators and inhibitors of plasmin
- Example: (activator) tissue type plasminogen activator (tPA) released by endothelial cells at site of injury

Simplified Coagulation Cascade
**Extrinsic Pathway of Coagulation**

- Factor III (tissue thromboplastin) released by damaged tissue cells; allowing a chemical shortcut
- Pathway is rapid (12-15 seconds)
- Forms a small amount of thrombin

**Intrinsic Pathway of Coagulation**

- Slower pathway (5-10 minutes)
- Forms larger amount of thrombin

Extrinsic and intrinsic pathways merge into the common pathway
- Goal: formation of fibrin network trapping cells and platelets producing a thrombus

**Case Scenario**

- Patient is a 67 y/o Caucasian male referred for functional crown lengthening for tooth #19 and implant placement #12
- Patient's medical history includes atrial fibrillation and a mechanical mitral valve
- Current cardiovascular medications include: (note two antithrombotic medications)
  - Aspirin 81 mg.
  - Warfarin (Coumadin®)
  - Metoprolol 25 mg.

How are you going to manage this patient?
Indications include the prevention or treatment of thromboembolic (TE) events for the following patients:
- Coronary artery stents
- Atrial fibrillation
- Deep venous thrombosis (DVT)
- Pulmonary embolism
- Mechanical heart valve(s)
- Cerebrovascular disease

Pre-operatively discontinue the antithrombotic medication(s) 5-7 days prior to surgical procedure
Restart the antiplatelet or anticoagulant medication one to several days after procedure
This approach places patients at higher risk for thromboembolic event (potentially fatal complication)

In 1996, 56% of physicians routinely discontinued an anticoagulant in patients scheduled for single tooth extraction (1)
In 2007, about half of dental school faculty taught students to discuss discontinuing warfarin with physicians in preparation for tooth extraction(s) (2)

(2) Lindhout et al. J Dent Educ 2007
Questioning the Traditional Approach

- M. Wahl (Archives of Internal Medicine, in 1998) reviewed literature on dental surgical procedures performed while patients on continuous warfarin therapy (some with supratherapeutic INR)
- Included multiple and surgical extractions
- Over 98% of patients had no serious bleeding
- Minor bleeding controlled with local measures
- No well documented cases of serious bleeding
- Are documented cases of serious/fatal embolic events in patients discontinuing warfarin therapy.

Wahl M. Arch Intern Med 1998

Pre-surgical Patient Assessment

- Recommend careful patient history including family history and experience with dental surgery, medical surgery and following injury
- Include OTC medications and herbal supplements
- Medical consultation with patient’s physician
- May include evaluation of patient’s liver and kidney functions
- Underlying consideration: weigh risk of bleeding during and after dental procedure vs. risk of TE event if modify medication dose or discontinue medication short term

Patient Considerations

- If patient continues on their antiplatelet or anticoagulant medication, can I manage bleeding with these measures:
  - Direct pressure application
  - Sutures
  - Periodontal dressing
  - Topical agents ex. oxidized cellulose, gelatin sponge, collagen sponge, topical thrombin, and prescription oral rinses
- Anticipate additional treatment time
- Strongly consider localized surgical procedure
- Emphasize strict patient compliance with postsurgical instructions (oral & written instructions)
Antiplatelet Medications
- Aspirin
- Clopidogrel (Plavix®)
- Ticlopidine (Ticlid®) - uncommon use
- Prasugrel (Effient®)
  - Drug of choice to prevent and treat arterial thrombosis
  - Mechanism of action: impair platelet aggregation and inhibit thrombus formation
  - Commonly used post coronary artery stent placement
What About Bleeding Time Test?

- Traditionally, bleeding time (ex. Ivy bleeding time) with cutaneous incision suggested
- Ivy test is an expensive and technique sensitive assay
- New lab test available: Platelet Function Assay (PFA) which measures platelet adhesion and aggregation (measures primary hemostasis)
- Platelet Function Assay may become more widely used in future

Current Bleeding Test Guidelines

- In 1998, College of American Pathologists and American Society for Clinical Pathology issued this guideline:
- In absence of history of bleeding disorder, bleeding time not a useful predictor of hemorrhage risk associated with surgical procedures

Antiplatelet Considerations

- Physician prescribed or patient prescribed?
- Is patient on dual antiplatelet medications?
- Aspirin, clopidogrel, ticlopidine and prasugrel irreversibly inhibits the platelet function
- Antithrombotic effect lasts for about 7 days
- A 2007 Medical Advisory states to continue patient on dual antiplatelet therapy for at least 12 months after placing drug-eluding coronary artery stents
Limited literature evidence regarding bleeding complications following periodontal treatment
Limited literature evidence regarding bleeding complications with dental implant placement
Most studies evaluated bleeding complications following tooth extractions (generally ≤ 5 teeth)

Antiplatelet Evidence

- Randomized control trial with ninety-six patients on 100 mg. daily aspirin
- One patient group discontinued aspirin 7 days pre-surgical (other group continued)
- Open flap debridement surgery
- Local hemostatic measures (cellulose gauzes) utilized
- No significantly higher risk of postsurgical bleeding between groups

Siebert et al. AAP Poster Presentation 2011

Antiplatelet Evidence (2)

- Forty-three patients on single or dual antiplatelet therapy
- Dental procedures included ScRP, tooth extraction (mean of 5 teeth), alveoplasty, periodontal surgery and implant surgery
- Local hemostatic measures utilized
- Oral bleeding complication were “negligible”

Napeñas et al. J Am Dent Assoc 2009
Literature Review - Antiplatelets

- Included case-control and cohort studies, and randomized controlled trials (1948 - 2011)
- Authors noted “minor” immediate postop. bleeding (<60 minutes)
- No clinically significant intraoperative or late postoperative bleeding complications
- Local hemostatic measures adequately controlled bleeding
- No indication to alter or D/C antiplatelet medications


Novel Oral Antiplatelet Medications

- Introduced in 2009
- Prasugrel (Effient)
- Ticagrelor (Brilinta)
- Based on literature review by Johnston always weigh risk of dental surgical bleeding vs. risk of thromboembolic event if discontinue antiplatelet medication (medical consult).
- Johnston favors continuing antiplatelet therapy during dental surgery.


Anticoagulant Medications

- Warfarin (Coumadin®), Vitamin K antagonists (VKA)
- Heparins
- Dabigatran (Pradaxa®)
- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)
- Edoxaban (Savaysa®)
Atrial Fibrillation
- Most common dysrhythmia seen by physicians
- Currently, 2.5 million patients in U.S.
- 10 – 14% of population age 80 or older
- Risk increased with chronic medical conditions (and aging)
  - Hypertension
  - Diabetes mellitus
  - Heart Failure
  - Obesity
  - Sleep apnea
  - Hyperthyroidism

Blood pooling in left atrium leads to thrombus formation (left atrial appendage)
- Five fold increased stroke risk
- One third of patients have “silent” A Fib.
- Women have higher risk of stroke
- 15-20 % of strokes caused by A Fib.
- Strokes are especially debilitating or fatal

Stroke Risk Calculation with Atrial Fibrillation
- CHADS₂ score (congestive heart failure, hypertension, age 75, diabetes mellitus, stroke or transient ischemia attack [TIA] history)
- Low risk (score 0) aspirin
- Intermediate risk (score 1) aspirin or OAC
- High risk (score 2) OAC
- Approximately 40% of A fib. patients with “significant” risk are not on anticoagulant therapy
Updated Risk Calculation for Atrial Fibrillation Patients

- Improved stroke risk assessment
- CHA2DS2 - VASc (vascular disease, age, sex category)
- Score of 2 or greater, oral anticoagulant recommended

Warfarin (Coumadin)

- **Intrinsic Pathway**
  - FXlla - FXa - FIXa
  - FXa (HFIXa)
  - FII (prothrombin) - FIIa (thrombin)
  - Fibrinogen - Fibrin

- **Extrinsic Pathway**
  - FVIIa + Tissue Factor

Warfarin

- Long term history in medicine (since 1950's)
- Inhibits vitamin K dependent factors (II, VII, IX, X) and regulatory proteins C and S
- Very long half life, up to 42 hours
- Extensive interactions with diet and over 200 medications
- Requires regular monitoring to measure degree of anticoagulation
- Superior prevention of stroke over aspirin
**International Normalized Ratio (INR)**

- PT measures warfarin level of anticoagulation
- Designed to standardize prothrombin time (PT) between medical labs

\[
\text{INR} = \left( \frac{\text{Patient's PT}}{\text{Normal PT}} \right)^{\text{ISI}}
\]

ISI - International Sensitivity Index

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**Warfarin (2)**

- Most patients – recommended therapeutic INR range is 2.0 – 3.0 (target = 2.5)
- Some patients “high intensity” INR range of 2.5 – 3.5 (ex. mechanical heart valve) with target of 3.0
- About 1/3 of warfarin patients are outside therapeutic range
- Recommend PT/INR within 24 hours of planned surgical procedures

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**Warfarin (3)**

- Commonly prescribed analgesics, antifungals, and antibiotics may interact with warfarin, often increasing the INR
- Return patient to physician for new PT/INR within 3 days of prescribing above medications
- What about a single antibiotic dose for infective endocarditis prophylaxis?
Warfarin - Drug Interactions
- Aspirin and other NSAID contraindicated
- Acetaminophen has potential to increase INR
- Evidence: acetaminophen 325 mg. q.i.d. for one week increased INR in some patients
- Recommendation: after 3 days of “regular” acetaminophen intake, recommend new INR

Management of Warfarin Patient
- Anticoagulant effects lasts for 5 days
- Traditional approach is to hold warfarin for 5 days and resume warfarin 2 days postsurgery
- Medical consultation to weigh risk of stopping or reducing dose of warfarin vs. thromboembolic risk for patient

- Patients with mechanical heart valves, A. fib or thromboembolism (TE)
- High risk for TE – bridge with heparins
- Moderate risk for TE – consider heparins
- Low risk for TE – either low dose heparin or unnecessary for 4-5 day interruption of warfarin

Guyatt et al. Chest 2012
Discontinue warfarin 5 days presurgical
- Bridge anticoagulation with unfractionated heparin (UFH) or low molecular weight heparins (LMWH)
- (UF) heparin usually inpatient procedure with I.V. therapy and assess level of anticoagulation with aPTT (activated partial thromboplastin time)
- LMWH therapy often as outpatient therapy

Heparin

Extrinsic Pathway
FXa + Tissue Factor

Intrinsic Pathway
- FXIIa
- FXIa
- FIXa

Low Molecular Weight Heparin

Low Molecular Weight Heparin

Heparin =
Low Molecular Weight Heparin

• Improved bioavailability effect over heparin
• Sub Q injection one or two times daily
• Usual dose: 1 mg/kg body weight
• Typically don’t assay anticoagulant level
• Lab test available: anti-FXa assay
• Short half life of 2-4 hours
• Hold LMWH the day of planned surgery
• Resume LMWH and warfarin within 24 hours (with physician directions)

When Warfarin is Continued

Tranexamic Acid (Cyclokapron®)

• Continue patient on their anticoagulant
• Anti-fibrinolytic medication
• Oral rinse has short half-life, prepared by pharmacy day prior to surgery or dispensed by dentist
• Expensive, may require compounding pharmacy to dispense ($190)
• Formula: 10 mg. powder in 200 ml water
• Sig: rinse with 2 tsp. (10 ml) for 2 minutes pre-op, at end of procedure and q.i.d. until gone
Aminocaproic acid (Amicar®)
- Available as IV solution, 25% oral rinse and tablet
- Inhibits fibrinolysis
- In acute bleeding episode, use 4 tsp. stat, then 1 tsp. per hour
- For hemostasis following dental extractions in hemophilia patient, dose of 50-60 mg/kg every 4 hours

Evidence – Antithrombotic Medication Patients
- 139 patients underwent ScRP, gingivectomy and open flap debridement procedures
- Oxidized cellulose placed, flaps sutured and 10 minutes gauze pressure used for hemostasis
- Periodontal dressing and electrocautery used as needed
- Postoperative bleeding in only 1.3%
- Antiplatelet group - therapy safe for all
- Anticoagulant group – surgery safe if INR <3.0

Evidence – Implant Therapy

- Case control study of long term warfarin patients (52 patients) and 109 control subjects
- Pre-op PT/INR confirmed in therapeutic range
- Two stage implant surgery
- Applied gauze soaked in tranexamic acid for 30 - 60 minutes after suturing
- Warfarin group – two late bleeding episodes controlled with local measures
- Control group – three late bleeding episodes managed with local measures

Bacci et al. COIR 22:151, 2011

Literature Evidence – Tooth Extraction(s)

- Study of 142 patients continuing oral anticoagulant (INR mean of 2.5, up to 3.9) and low dose aspirin (100mg.) therapy
- One to four tooth extractions (a few cases of surgical extraction involving flap elevation
- Teeth extracted due to caries or periodontitis
- Extraction sockets packed with collagen sponge, local pressure applied and sutures, if necessary
- Reported only five cases of postop bleeding

Bajkin et al. JADA 143, 2012

Evidence – Implant Therapy

- Systematic review by Madrid and Sanz
- Minor oral surgery i.e. single tooth extraction can be safely performed in anticoagulated patient
- Concluded “dental implant placement is less traumatic than extraction of three teeth”, unless harvesting autogenous bone, elevating extensive flaps or inadvertently prepare osteotomy outside alveolar housing

Clinical Case Example #1
- 74 y/o male underwent four sextants/quadrants of flap and osseous sx.
- Significant med. hx. – atrial fibrillation
- Continued on warfarin therapy during four surgical procedures (INR range of 1.9 – 2.4)
- Hemostasis achieved by direct pressure with saline moistened gauze
- Consider use of periodontal dressing
- Prolonged observation prior to dismissal
- No excessive bleeding postop

Clinical Case Example #2
- 82 y/o female scheduled for 3 implants with alveoplasty and extraction of 6 teeth (2 appts.)
- History of pulmonary embolism and deep venous thrombosis (separate events)
- Managed on warfarin, but discontinued by MD
- Placed on LMWH bridge (held day of surgery)
- Preop INR 1.5 for both surgeries
- Procedure completed with no significant postoperative bleeding

New Oral Anticoagulants
- Xarelto
- Eliquis

[Images of Xarelto and Eliquis tablets]
“New” Oral Anticoagulants

- Pradaxa®
- Xarelto®
- Eliquis®
- Savaysa®
- Approved for non-valvular atrial fibrillation, and prevention/treatment of venous thromboembolism (deep venous thrombosis and pulmonary embolism)

New / Novel / Direct Oral Anticoagulants

- Together referred as NOAC or DOAC (direct oral anticoagulants)
- Much higher cost than warfarin
- No specific commercial laboratory test available to assess level of anticoagulation
- Currently, only Pradaxa (dabigatran) has an approved reversal agent (as of October 2015)
- Reversal: Praxbind (idarucizumab) $$$
- Others awaiting FDA approval of reversal agent

Dabigatran (Pradaxa)
Dabigatran (Pradaxa)
- FDA approved in 2010
- Direct thrombin inhibitor (Factor II)
- Two hour onset of anticoagulation
- Short half life of 14-17 hours
- Dose of 150 mg b.i.d. (75 mg b.i.d. if impaired kidney function)
- Predictable anticoagulation response
- No laboratory monitoring recommended

Rivaroxaban (Xarelto)
- FDA approved in 2012
- Factor Xa inhibitor
- Four hour peak activity
- 5-9 hour half life
- Usual dose: 20 mg daily (15 mg, with significant kidney impairment)
Apixaban (Eliquis)

- FDA approved in 2012
- Factor Xa inhibitor
- Three hour onset
- 8-15 hour half-life
- Usual dose: 10 mg b.i.d.
- 2.5 mg b.i.d. if patient ≥80 y/o, body weight less than 60 kg. or reduced kidney function

Edoxaban (Savaysa)

- FDA approved in 2015
- Factor Xa inhibitor
- Dose of 60 mg daily (reduced to 30 mg with impaired kidney function, verapamil, quinidine, azithromycin, clarithromycin, erythromycin, and oral ketoconazole use)
- Onset of 1-2 hours, half life of 10-14 hours
Considerations in Patient Management (DOACS)

- Lack long term track record of use
- "Limited" antidote available in emergent situation
- No specific commercial lab test to assess level of anticoagulation
- Currently available lab tests may be unreliable (ex. no INR help)
- Medical consultation recommended for discontinuing these oral anticoagulants

Current Guidelines for New Meds

- Consider continuing anticoagulants for sx.
- Currently no data on when to discontinue
- For "standard" bleeding risk, discontinue 24 hours pre-op (48 hours or longer if kidney function impairment)
- For "high risk bleeding" (ex. general, cardiac surgery, discontinue 2-4 days and longer with kidney function impairment)
- Restart anticoagulants when risk of postop. bleeding minimal (stable fibrin clot)- usually 24-48 hours

Recommended Guidelines for DOAC

- Dental management guidelines similar to those taking warfarin, esp. LMWH
- Consider continuing the direct oral anticoagulant during "uncomplicated tooth extractions"
- Utilize adjunctive local hemostatic measures (direct gauze pressure, absorbable gelatin, oxidized cellulose, sutures, and prescribed oral rinses

117 patients underwent single implant placement, multiple implants, guided bone regeneration and lateral wall sinus augmentation procedures while on antiplatelet or anticoagulation medications.

- **Anti-thrombotic management:**
  - 30 patients continued warfarin
  - 8 patient bridged on LMWH
  - 63 patients continued antiplatelet medication(s)
  - 16 patients continued DOAC

Bleeding risk low in this patient population. Total of four cases of postoperative bleeding complications (usually within 24 hours postop)

- Two cases in warfarin group, one in LMWH bridge group and none in DOAC group
- Bleeding complications managed with local measures (wound compression with tranexamic acid gauze, additional suturing, or wound revision with electrocautery)

In summary, surgical intervention including periosteal releasing incision increased bleeding risk.

- Authors recommended electrocoagulation following periosteal releasing incision
- No thromboembolic complications occurred during study period
General Recommendations

- Determine if antiplatelet and or anticoagulant therapy is short or long term
- Consider delaying dental surgery if short term medication is planned
- Importance of a medical consultation to assess TE risk and possible modification of antithrombotic med.
- Consider localized, conservative surgical procedures
- Schedule procedure early during the week
- Schedule early morning surgical appointment

Case Scenario

- Patient is a 67 y/o Caucasian male referred for functional crown lengthening for tooth #19 and implant placement #12
- Patient's medical history includes atrial fibrillation and a mechanical mitral valve
- Current cardiovascular medications include:
  - Aspirin 81 mg.
  - Warfarin (Coumadin®)
  - Metoprolol 25 mg.

How are you going to manage this patient?

Questions
Clinical Case Example #3

- 71 y/o male
- History of embolism with Xarelto anticoagulation
- Medical consult with physician who recommended discontinuing anticoagulant 24 hours preop
- Extraction of tooth #6 with immediate implant placement
- No significant perioperative or postop bleeding
1. The correct order (from initial to final phase) of phases of hemostasis is:
   a. Platelet – Vascular – Coagulation
   b. Vascular – Platelet – Coagulation
   c. Coagulation – Vascular – Platelet
   d. Vascular – Coagulation – Platelet

2. Which of the following is NOT a medical condition commonly managed with an antithrombotic medication?
   a. Hemophilia A
   b. Atrial fibrillation
   c. Deep venous thrombosis
   d. Pulmonary embolism

3. All of the following medications are antiplatelet agents EXCEPT:
   a. Aspirin
   b. Clopidogrel (Plavix)
   c. Low molecular weight heparin
   d. Prasugrel (Effient)

4. Most patients on warfarin (Coumadin) are maintained in a therapeutic range of
   a. 1.0 – 2.0
   b. 2.0 – 3.0
   c. 3.0 – 4.0
   d. 4.0 – 5.0

5. Which of the following medication is NOT a novel or direct oral anticoagulant
   a. Dabigatran (Pradaxa)
   b. Rivaroxaban (Xarelto)
   c. Enoxaprin (Lovenox)
   d. Apixaban (Eliquis)

6. The degree of anticoagulation for patients taking apixaban (Eliquis) can be accurately determined with the international normalized ratio (INR) blood test.
   a. True
   b. False
KEY: 1. b  2. a  3. c  4. b  5. c  6. False