Bleeding Disorders

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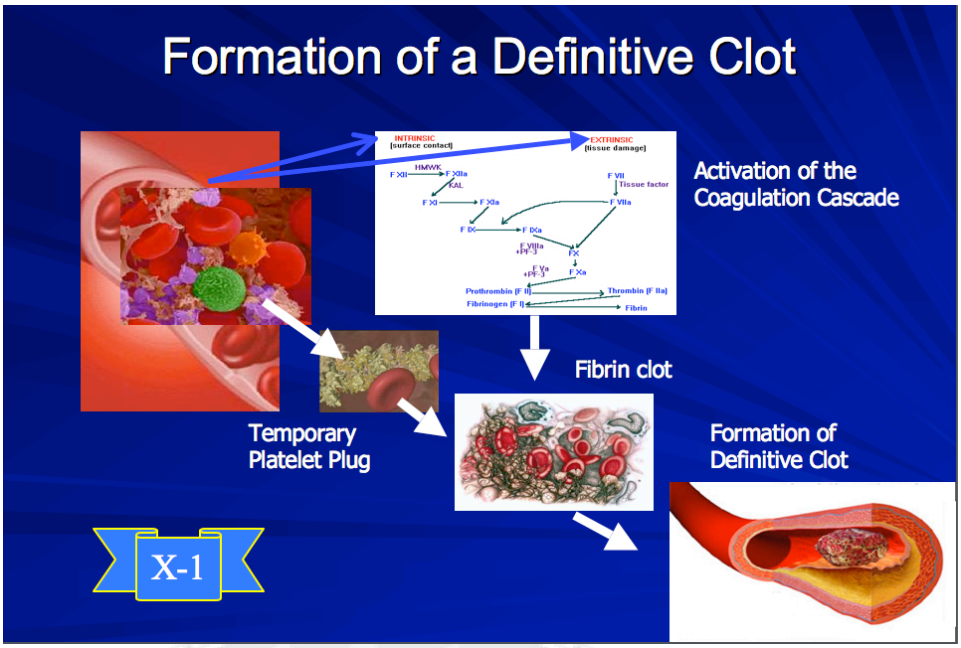
Formation of a definitive clot is a complicated process involving a number of physiologic events. When a blood vessel is damaged, marked vasoconstriction results. Platelets adhere to the damaged surface and aggregate to from a **temporary hemostatic plug**. Through two separate pathways, the intrinsic and the extrinsic pathways, involving a cascade of 12 circulating plasma proteins called clotting factors, the conversion of fibrinogen to fibrin is completed. Fibrin binds to the aggregated platelets to form a **definitive hemostatic clot**.

Finally, anti-clotting mechanisms in the fibrinolytic pathway are activated to prevent propagation of the clot and to allow for clot dissolution and repair of the damaged vessel. The fibrinolytic pathway is designed to limit the amount of clot that can form during the healing process. Successful hemostasis is therefore dependent upon adequate numbers of platelets, proper functioning of the platelets, adequate levels of clotting factors, and proper functioning of the fibrinolytic pathway.

In brief, platelets are responsible for the formation of a temporary plug and clotting factors are responsible for the formation of a permanent clot.

Bleeding can be the result of inability to form a temporary clot or the inability to form a definitive clot. Inability to form a temporary clot results from **inadequate platelet count (thrombocytopenia)** or **abnormal platelet function (thrombocytopathy)**. Inability to form a definitive clot results from **abnormalities in the clotting factors**.



Platelet Disorder

The platelet count provides a quantitative evaluation of platelet function. The normal platelet count should be 100,000 to 400,000 cells/mm3. A platelet count of less than 100,000 cells/mm3 is called thrombocytopenia. Mild thrombocytopenia (platelet count of 50,000 to 100,000 cells/mm3) can result in abnormal bleeding post-operatively. Severe thrombocytopenia (less than 50,000 cells/mm3) can be associated with major post-operative bleeding and platelet transfusion is often necessary prior to any dental intervention.

Bleeding Disorders Secondary to Decreased Platelets

In general, conditions that result in decreased platelet orders are quite uncommon.

Bleeding Disorders Secondary to Abnormal Platelet Function

Abnormal platelet function (thrombocytopathy) indicates that despite normal number of platelets, the platelets do not function normally and form a temporary hemostatic plug ineffectively, with resultant clinical bleeding.

Abnormal platelet function can be assessed by the Ivy Bleeding Time. The bleeding time provides an assessment of the adequacy of platelet count and function. The test measures how long it takes

a standardized skin incision to stop bleeding by the formation of a temporary plug. Using the standard Ivy method, the normal bleeding time is 5-9 minutes. The bleeding time is prolonged in patients with either thrombocytopenia or abnormal platelet function. This test is seldom invoked since the majority of patients with abnormal platelet function is already known to be on drugs that can cause platelet abnormalities: For example, a patient taking aspirin or Plavix may have bleeding time of 9-12 minutes. This can lead to mild intra-operative and post-operative bleeding.

Thrombocytopathy (abnormal platelet function) can be the result of either inherited or acquired disorders.

Inherited disorders account for less than 1% of patients who present with abnormal platelet function. The most common among these inherited disorder is von Willebrand's disease. In this disease, not only is there an abnormality in the function of platelets, there is also a deficiency in the production of Factor VII. Patients with this disease can therefore bleed both from a platelet abnormality and from Factor VII deficiency. The platelet function abnormalities in von Willebrand's disease can be corrected by administration of DDAVP.

Acquired disorders of platelet function are far more common than inherited disorders.

a. **Drug-induced defects:** by far the most common reason for thrombocytopathy is drug-induced thrombocytopathy. **Aspirin** and aspirin containing compounds are the most common drug to cause platelet function abnormalities. Aspirin inhibits cyclo-oxygenase 1 and 2 enzymes in the platelets in an irreversible fashion, resulting in decrease in formation of prostaglandin precursors. Once a platelet is exposed to aspirin, its function is irreversibly compromised. The effect of aspirin in susceptible patients therefore lasts the lifetime of the platelet population exposed. Patients exposed to even small doses of aspirin can have platelet function abnormalities for 7-10 days. This is not a dose-dependent phenomenon and patients on 81 mg of aspirin can have as much platelet function abnormality as a patient taking a much higher dose.

   Plavix is an agent that irreversibly blocks the $P2Y_{12}$ component of the ADP receptors on the platelet surface which prevents GPIIb/IIa receptor complex, thereby reducing platelet aggregation. Plavix would cause platelet function

abnormalities for 7-10 days after last exposure. Plavix is used in a number of situations:

Patients with coronary disease
Patients with cerebrovascular disease
Patients with peripheral vascular disease
Patients with coronary stents

Plavix was originally envisioned by be more efficacious with less bleeding complications but this has not been substantiated in clinical trials.

One trial comparing Plavix vs ASA + PPI showed that the patients on Plavix had more bleeding complications.

Combination of **ASA and Plavix** is often employed, particularly during the first 6 months after stent placement. Combination therapy has also been invoked in a variety of other circumstances: in the CURE study, patients with acute coronary syndrome had better outcome on combination therapy but the combination was more likely to cause bleeding complications. In the CHARISMA study, addition of Plavix to ASA in patients with established vascular disease or multiple risk factors showed no benefit over ASA alone. Combination was associated with increased bleeding.

A recent study on single therapy vs combined therapy in patients with strokes showed that there was not additional benefit from combined therapy. There was an increased risk of bleeding complications in patients on combined therapy. This study was terminated early because of these findings.

A recent study in patients following CABG showed better saphenous vein graft patency, particularly in off pump bypass cases. However, patients on combined therapy had significantly more bleeding complications, making risk benefit evaluation difficult.

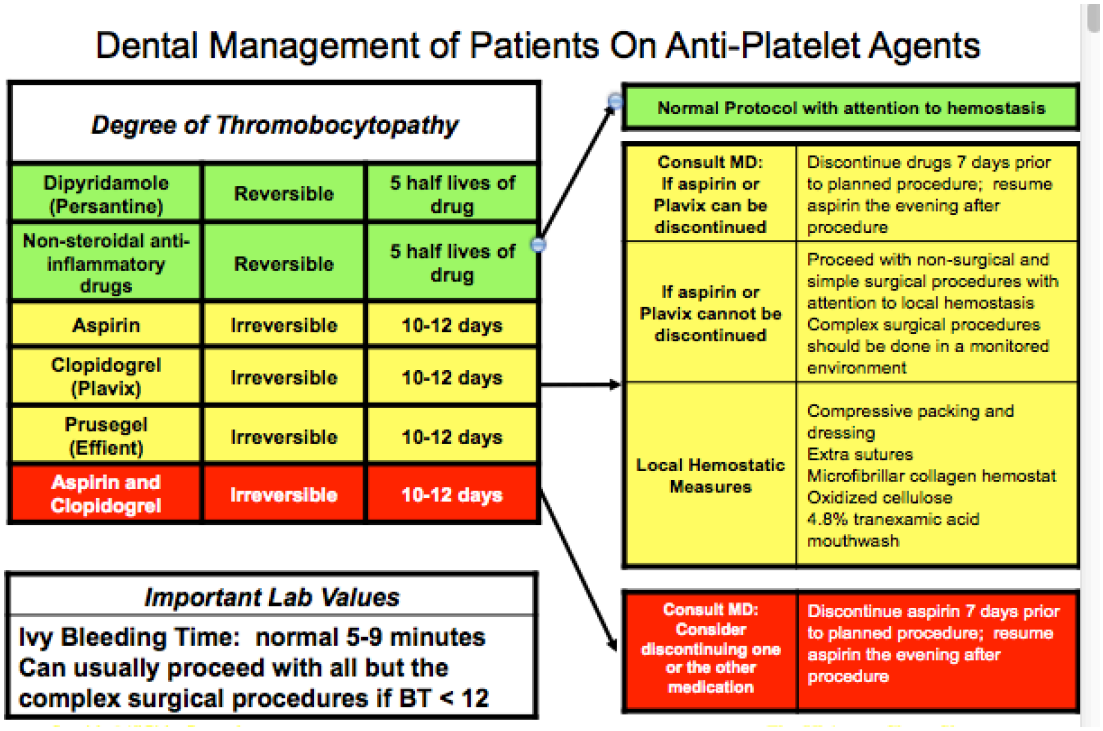
New Anti-platelet Agent: Prasugel (Effient)

Prasugel (Effient) is a new anti-platelet agent that is similar to Plavix and is usually used in patients after percutaneous coronary intervention or in patients with known Plavix allergy.

Non-steroidal anti-inflammatory drugs, on the other hand, causes reversible inhibition of cyclo-oxygenase 1 and 2. The effect of the non-steroidal anti-inflammatory drugs on platelet function therefore lasts only the lifetime of the drug and thrombocytopathy is usually reversed 24 to 48 hours after the last exposure to the drugs.

The COX-2 specific inhibitor (Celecoxib, Celebrex) does not affect platelet function.

Concurrent ingestion of alcohol after aspirin or non-steroidal anti-inflammatory drug exposure can markedly enhance thrombocytopathy.



Drugs to avoid in patients on anti-platelet agents include:

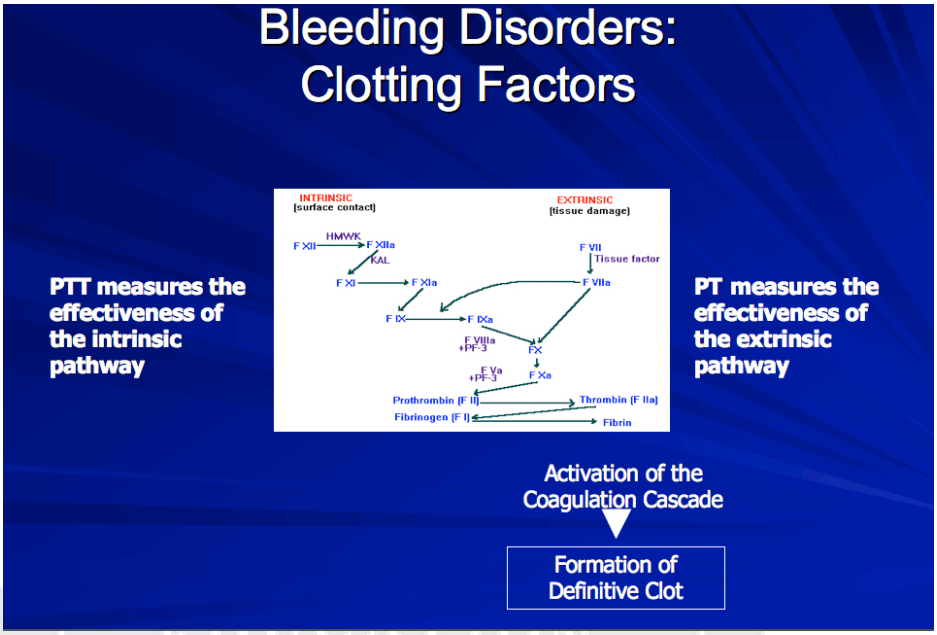
- Aspirin
- Non-steroidal anti-inflammatory drugs

Drugs that are safe include:

- All antibiotics
- Acetaminophen
- Celecoxib
- All narcotics
- All commonly used sedatives

Bleeding Disorders secondary to Clotting Factor Issues

Two tests, the prothrombin time (PT) and the partial thromboplastin time (PTT), provide a reasonable measure of the integrity of the clotting factors.



The prothrombin time (PT) measures the effectiveness of the extrinsic pathway to mediate fibrin clot formation. A normal PT indicates normal levels of Factor VII and those factors common b both to the intrinsic and the extrinsic pathways (V, X, prothrombin, and fibrinogen). PT can be expressed in a number of ways: as PT in seconds or as INR, which is the most accurate way of following PT. INR takes into account of reagent variability and allows for the most accurate monitoring of PT. A normal INR is 1 and an INR above 2 would usually denote coagulopathy.

Patients taking coumadin have a prolonged PT/INR because of the interference of coumadin with the synthesis of vitamin K clotting factors. PT/INR is monitored frequently in these patients (weekly to monthly). A normal therapeutic range of INR would usually be in the 2-3 range. Patients requiring high-intensity anticoagulation may have INR in the 2.5 to 3.5 range.

Coagulation factor deficiency is due either to a congenital disorder or an acquired disorder.

A number of **congenital clotting factor deficiencies** have been described, but three diseases, Hemophilia A (Factor VIII deficiency), B (Factor IX deficiency) and von Willebrand's disease, account for more than 90% of all inherited coagulation factor deficiencies.

Far more common than congenital factor deficiency is **acquired factor deficiency**.

Deficiency of vitamin K-dependent coagulation factors is the most common acquired disorder of coagulation. Factors II (prothrombin), VII, IX and X are made in the liver and require vitamin K for synthesis of their active forms. Among these factors, Factor VII has the shortest half-life (3 to 5 hours). Therefore, prolongation of PT (which measures Factor VII activity) is the first indicator of deficiency of vitamin K-dependent factors. Common causes of acquired disorders of coagulation include:

Oral anticoagulants: Coumarin anticoagulants competitively inhibit vitamin K action. Patients on anticoagulants will therefore have a prolonged PT.

Liver disease: with significant liver disease, synthesis of a number of coagulation factors is impaired. Vitamin K-dependent factors (II, VII, IX and X), as well as Factors I and V are all synthesized by the liver. Patients with severe liver disease can therefore have significant compromises of their ability to clot.

Dental Management of Patients on Coumadin Therapy

Indications for anticoagulation	
Atrial fibrillation	INR 2-3
Deep venous thrombosis	INR 2-3
Pulmonary Embolism	INR 2-3
Prosthetic valve	INR 2.5-3.5
Hypercoagulable states	INR 2.5-3.5

Important Lab Values
Normal INR 1

For most non-surgical and surgical procedures	**Check INR prior to procedure** **If INR is 2-2.5:** Proceed with attention to local hemostatic measures **If INR is > 2.5:** Consult MD and allow INR to drift down to safe range
Local Hemostatic Measures	Compressive packing and dressing Extra sutures Microfibrillar collagen hemostat Oxidized cellulose 4.8% tranexamic acid mouthwash **Topical thrombin**

Non-surgical and simple surgical procedures	**INR 2.5 - 3.5**	**Proceed with attention to local hemostatic measures, including use of topical thrombin**
Complex surgical procedures	**INR 2.5 - 3.5**	**Consult MD** **Transient use of Fragmin for bridging** **Hold Fragmin on morning of procedure** **Resume Fragmin on evening of procedure** **Monitor PT/INR until patient is back in range**

Medical Management of Patients with Bleeding Disorders

For patients with platelet count much less than 50,000, platelet transfusions would be appropriate before major surgery

Aspirin and Plavix irreversibly inhibits platelet adhesiveness and would therefore inhibit the platelets for its lifetime. In order to prevent thrombocytopathy of these drugs, the drugs should be stopped for a week to 10 days before the procedure

Non-steroidal anti-inflammatory drugs inhibit cyclo-oxygenase reversibly and its thrombocytopathic effect would wear off as the drug effect wears off. Stopping non-steroidal anti-inflammatory drug for a day is usually adequate for the thrombocytopathy to wear off.

For patients with hemophilia, factor replacement should be undertaken prior to surgical procedures, particularly in instances of severe factor deficiency.

For patients with prolonged PT/INR secondary coumadin therapy or liver disease, this can be corrected slowly with vitamin K injections or rapidly with FFP transfusion.

Dental Evaluation of Patients with Bleeding Diathesis

Case #1

54 year old patient comes in seeking oral conscious sedation. He needs removal of the third molar. He gives a history of excessive bleeding with all of his previous dental procedures. He actually had to go to the hospital for transfusion on his last extraction.
Medical history is remarkable for hypertension for which he is on Cardura 4 mg bid.

What additional information do you need?

_____
_____
_____
_____
_____

In general, CBC with platelet count, bleeding time, PT and PTT should address most of the concerns with hemostasis. In rare instances, specific tests such as platelet aggregation tests or Factor levels may be appropriate. The latter tests have to be coordinated with the patient's physician. These tests should be considered in patients with known risks:

1. A patient giving a strong personal or family history of bleeding should be screened.
2. A patient known to be on medications that can cause thrombocytopenia should be screened.
3. Patients with prior history of illnesses that can interfere with hemostasis should be screened (ITP, TTP, etc)
4. Patients on coumadin have to be screened.

Case #1

CBC normal
Platelet count 220,000
Ivy bleeding time 5 minutes
PT/INR 12/1.0
PTT <25 seconds

Detailed family and personal history are negative in detail.

What should you do?

_____
_____
_____
_____
_____

Case 2

54 year old gentleman with history of coronary artery disease comes in for consideration of oral conscious sedation. He has had two stents placed 2 years ago

PMH significant for hypertension and hyperlipidemia

Medications
ASA 325 qd
Plavix 75 qd

Crestor 10 qd
Lisinopril 10 qd
Toprol XL 100 qd

He needs to have
Scaling and polishing of maxillary teeth
Caries removal
RTC 6,7
Maxillary teeth prepped and provisionalized

Anticipated to need 4 hours of surgery

What is his ASA status?

What should you do?
_____
_____
_____
_____
_____

1. Most of the problem with thrombocytopathy that the dentist would encounter comes from exposure to drugs that can impair platelet function. The most common drugs include aspirin, Plavix and non-steroidal anti-inflammatory drugs. Stopping these drugs at appropriate intervals prior to dental intervention should reverse the thrombocytopathy.
2. In instances where the patient has a known underlying disease causing thrombocytopathy, careful attention to hemostasis should be employed. Specific recommendations depend upon the underlying disease and the degree of the platelet function abnormalities.
3. Combined ASA and Plavix can cause excessive bleeding
4. It is important not to stop Plavix abruptly in a patient with a coronary stent since there are a number of reports of acute stent thrombosis
5. In patients with both ASA and Plavix, the physician should be consulted: usually one of the agents (usually ASA) cab be stopped
6. Local measures that will help hemostasis should be employed.

There are a number of local measures that can help hemostasis:

1. Compressive packing and dressing
2. Extra sutures
3. Microfibrillar collagen hemostat
4. Oxidized cellulose
5. 4.8% tranexamic acid mouthwash
6. Platelet concentrates

Case 3

64 year old gentleman in for consideration of oral conscious sedation.

PMH significant for hypertension, diabetes mellitus and atrial fibrillation.

Medications:

5 mg of coumadin qd
Enalopril 20 qd
Metformin 500 qd
Glyburide 10 qd

Anticipated time of surgery 4 hours

What is his ASA status?

What should you do?

_____
_____
_____
_____
_____

PT/INR is 2.2
BP 120/68
HbA1c 6.6%

His physician does not care one way or the other with respect to his holding coumadin.

What should you do?

_____
_____
_____

Case 4

54 year old patient with cirrhosis secondary to chronic alcohol excess comes in for consideration of oral conscious sedation

PMH significant for one bout of variceal bleeding necessitating transfusion of 4 units of blood. He has also had one admission for hepatic encephalopathy.

He needs 4 hours of surgery.

What is his ASA status?

_____

What additional information do you need?

_____
_____

What sedation protocol would you consider for Case 4?

_____
_____
_____
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