Anticoagulation and Antiplatelet Literature Review

By: Michael Martins

During my time at the hospital I have been exposed to many cardiac patients that all seem to be on a wide range of medications to manage their condition. This is done through a variety of different anticoagulation factors and antiplatelet drugs.

Blood clotting is a process that is normally trigger naturally in response to damage to blood vessels from injury or invasive procedures. Three phases of hemostasis exist: vascular, platelet and coagulation. The vascular and platelet phase are known as primary hemostasis and the coagulation phase is known as secondary. Coagulation phase is then followed by the fibrinolytic phase for which the clot is dissolved.

Vascular Phase

The vascular phase begins immediately after injury and involves vasoconstriction of the vessels, contraction and an increase in the extravascular pressure due to blood lost. This pressure aids in collapsing the adjacent capillaries and veins in the area. Vascular integrity plays a large role in maintaining the fluidity of blood. The smooth endothelial lining consists of a non-wettable surface that normally doesn't activate platelet adhesion or coagulation. These endothelial cells produce antiplatelet agents: prostacyclin, nitric oxide and certain adenine nucleotides.

Exposure of the vessels' subendothelial tissues, collagen and basement membrane initiates coagulation through the extrinsic pathway. These injured cells release adenosine diphosphate (ADP), which induces platelet adhesion and exposure of the subendothelial tissues bind to von Willebrand Factor (vWF) as well.

Platelet Phase

Platelets are cellular fragments that form from the cytoplasm of megakaryocytes and normally last 8 to 12 days in circulation. Platelets do not have a nucleus; thus, they are unable repair inhibited enzyme systems. The main function of the platelets is maintenance of vascular integrity, formation of a platelet plug to aid in initial control of bleeding and stabilization of the platelet plug. Subendothelial tissues become exposed and through contact activation cause the platelets to become sticky and adhere to these tissues. Platelet membrane glycoprotein Ib (GPIb) binds with vWF, which is attached to the subendothelial tissue, and glycoprotein Ia/IIa (GPIa/IIa) and glycoprotein VI (GPVI) bind to collagen in the injured vessel wall.

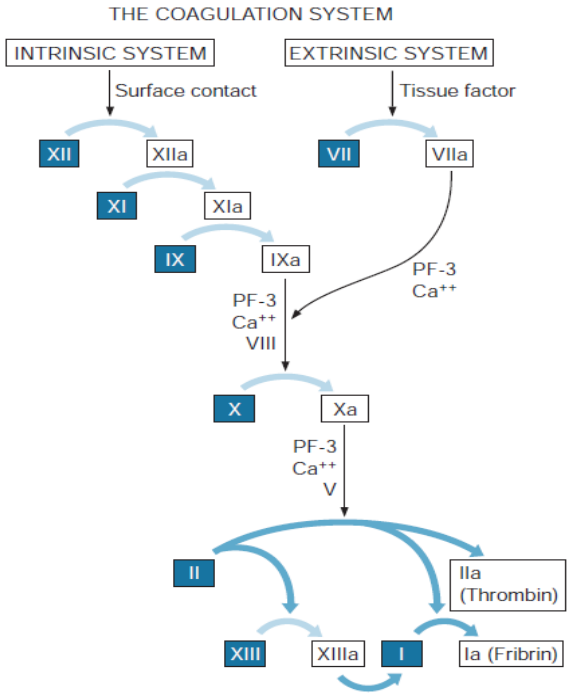
The ADP that was released in the vascular phase initiates the primary wave of platelet adhesion causing the platelets to secrete their own factors - known as the second wave of aggregation. One of these factors is thromboxane which is produced through cyclooxygenase. Aspirin acts as an inhibitor of cyclooxygenase, and this

causes irreversible damage to the platelets. This effect can last up to 9 days (time needed for the old platelets to be cleared from the blood). During the secondary wave, platelets bind with fibrinogen by the membrane glycoprotein IIb (GPIIb). Fibrinogen is then converted to fibrin, which stabilizes the platelet plug. The result of the preceding processes is a clot of platelets and fibrin attached to the subendothelial tissue

Coagulation Phase

This phase contains, platelets, blood proteins, lipids and ions. Thrombin is generated on the surface of the platelets which then converts bound fibrinogen to fibrin. The end goal of the coagulation phase is to produce this fibrin clot that will prevent further blood lost. This phase involves many components and factors. Many of the coagulation factors are proenzymes that become activated in a “waterfall” cascade. That means that once the process starts with one factor becoming activated, and it, in turn, activates another and so on, in an ordered sequence.

The intrinsic and extrinsic pathway meet into a common pathway to form the product, fibrin. The (faster) extrinsic pathway is initiated through tissue factor (an integral membrane protein) and is released or exposed through injury to tissues; this process activates factor VII (VIIa). As a result, thrombin is generated; in turn, fibrinogen is converted to fibrin. Thrombin generated by the faster extrinsic and common pathway is used to accelerate the slower intrinsic and common pathway. This is done through the activations of the factors in the common pathways like factor XIII, enhances factor V and factor VIII activity, and stimulates aggregation of additional platelets.



Fibrinolytic Phase

The fibrinolytic system is needed to prevent coagulation of intravascular blood away from the site of injury and to dissolve the clot, once it has served its function in homeostasis. This system involves plasminogen, a proenzyme for the enzyme plasmin, which is produced in the liver, and various plasminogen activators and inhibitors of plasmin. The prime endogenous plasminogen activator is tissue-type plasminogen activator (tPA), which is released by endothelial cells at the site of injury. The tPA released by injured endothelial cells binds to fibrin as it activates the conversion of fibrin-bound plasminogen to plasmin. Circulating plasminogen (i.e., not fibrin bound) is not activated by tPA. Thus, tPA is efficient in dissolving a clot without causing systemic fibrinolysis.

Assessing Bleeding Risk

Before providing dental treatment for a patient taking anticoagulants or antiplatelet drugs, their bleeding risk should be assessed. Three factors are involved in this consideration: dental procedure, medications and medical conditions.

Bleeding risks Associated with Different Dental Procedures

While the risk of bleeding complications associated with dental treatment for patients should be taken seriously, serious adverse bleeding events are rare. It was found that incidence of significant bleeding after dental procedures (defined as that requiring an unplanned intervention including repacking and re-suturing, or transfusion in extreme cases) for patients who have continued their warfarin therapy perioperatively, is estimated at less than 4%.

Below is table from the Scottish Dental Clinical Effectiveness Programme ranking procedures that increase the risk of bleeding

Dental procedures that are **unlikely to cause bleeding**	Dental procedures that are **likely to cause bleeding**	
	Low risk of post-operative bleeding complications	**Higher risk** of post-operative bleeding complications
Local anaesthesia by infiltration, intraligamentary or mental nerve block[a] Local anaesthesia by inferior dental block or other regional nerve blocks[a,b] Basic periodontal examination (BPE)[c] Supragingival removal of plaque, calculus and stain Direct or indirect restorations with supragingival margins Endodontics - orthograde Impressions and other prosthetics procedures Fitting and adjustment of orthodontic appliances	Simple extractions (1-3 teeth, with restricted wound size)[d] Incision and drainage of intra-oral swellings Detailed six point full periodontal examination Root surface instrumentation (RSI) and subgingival scaling Direct or indirect restorations with subgingival margins	Complex extractions[e], adjacent extractions that will cause a large wound or more than 3 extractions at once Flap raising procedures: • Elective surgical extractions • Periodontal surgery • Preprosthetic surgery • Periradicular surgery • Crown lengthening • Dental implant surgery Gingival recontouring Biopsies

Bleeding risks Associated with Different Anticoagulants and Antiplatelet Drugs

There is currently insufficient evidence to directly compare the relative bleeding risks associated with the various anticoagulants and antiplatelet medications for dental patients.

One known fact is that patients who are on dual or combination therapies and are taking more than one anticoagulant or antiplatelet drug are likely to have a higher bleeding risk than those on single drug therapies. However, once formed, the clot tends to be reasonably stable. The use of sutures at the time of treatment, in addition to hemostatic packing, usually stabilises the wound and may reduce the likelihood of prolonged or subsequent re-bleeding and the need for the patient to return for further treatment.

Bleeding Risks Associated with Different Medical Conditions

Certain medical conditions are known to be associated with increased bleeding risk. These include liver, kidney and bone marrow disorders. Although these effects are not dependent on the patient's anticoagulation medication, it is especially important for

the dentist to recognise these as additional risk factors that can contribute to post-operative bleeding.

Below is a table from the Scottish Dental Clinical Effectiveness Programme ranking listing the main medical conditions associated with increased bleeding risk.

Medical condition	Increased bleeding due to:
Chronic **renal failure**	Associated platelet dysfunction
Liver disease (e.g. caused by alcohol dependence, chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis)	Reduced production of coagulation factors. Reduction in platelet number and function due to splenomegaly. Alcohol excess can also result in direct bone marrow toxicity and reduced platelet numbers.
Haematological malignancy or myelodysplastic disorder	Impaired coagulation or platelet function (even in remission).
Recent[a] or current **chemotherapy**	Pancytopenia including reduced platelet numbers.
Advanced **heart failure**	Resulting liver failure.
Mild forms of **inherited bleeding disorders** including all types of haemophilia and von Willebrand's disease	Defective or reduced levels of coagulation factors.
Idiopathic thrombocytopenic purpura (ITP)	Reduced platelet numbers.

In addition to these medical conditions certain medications listed in the chart below can exacerbating a patient's bleeding risk.

Drug group	Effect
Other **Anticoagulants or antiplatelet drugs**[a] See Appendix 2 for listings.	Patients can be on dual, multiple or combined antiplatelet or anticoagulant therapies. These patients are likely to have a higher risk of bleeding complications than those on single drug regimes.
Cytotoxic drugs or drugs associated with bone marrow suppression[b] e.g. leflunamide, hydrochloroquine, adalimumab, infliximab, etanercept, sulfasalazine, penicillamine, gold, methotrexate, azathioprine, mycophenolate	These can reduce platelet numbers and/or impair liver function affecting production of coagulation factors.
Non-steroidal anti-inflammatory drugs (NSAIDs) e.g. aspirin, ibuprofen, diclofenac and naproxen	Impair platelet function to various extents.
Drugs affecting the nervous system Selective serotonin reuptake inhibitors (SSRIs) Carbamazepine	SSRIs have the potential to impair platelet aggregation and, although unlikely to be clinically significant in isolation, may in combination with other antiplatelet drugs increase the bleeding time. Carbamazepine can affect both liver function and bone marrow production of platelets. Patients most at risk are those recently started on this medication or following dose adjustment.

Warfarin or Other Vitamin K Antagonists

Mechanism of Action

Hepatic synthesis of coagulation factors II, VII, IX and X as well as protein C and S require the presence of vitamin K. These clotting factors are activated by the addition of carboxyl groups to key glutamic acid residues within the protein's structure. In the process, "active" vitamin K is oxidatively converted to an "inactive" form, which is then subsequently reactivated by vitamin k epoxide reductase complex 1 (VKORC1). Warfarin competitively inhibits the subunit q of the multi unit VKOR complex, thus depleting functional K reserves and hence reduces synthesis of active clotting factors.

Effects on Bleeding

Although warfarin is well established, substantial drug (antibiotics) and dietary (kale, spinach, brussels sprouts, parsley, collard greens, mustard greens, chard, green tea, and cranberry juice and alcohol) interactions exist and warfarin activity must be monitored frequently. This is achieved using the INR (international normalised Ratio) test. This test measures the time taken for a clot to form in a blood sample, relative to the standard. An INR value of 1 indicates a level of coagulation equivalent to that of an average patient not taking warfarin, and values greater than 1 indicate a longer clotting time and thus a longer bleeding time.

Recommendation

Patients taking warfarin or another vitamin K antagonist, with an INR below 3.5, treatment can be preformed **without** interrupting their anticoagulant medication.

Oral Antiplatelet drugs

ASA

Mechanism of Action

Irreversibly inhibits cyclooxygenase-1 and 2 enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A_2, via acetylation of platelet aggregation.

Clopidogrel (Plavix)

Mechanism of Action

Clopidogrel requires biotransformation to an active thiol metabolite. The active metabolite irreversibly blocks the $P2Y_{12}$ component of ADP receptors on the platelet surface. This prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Platelets blocked by clopidogrel are affected for the remainder of their lifespan.

Prasugrel (Effient)

Mechanism of Action

Prasugrel, an inhibitor of platelet activation and aggregation, is a prodrug that is metabolized to both active (R-138727) and inactive metabolites. The active metabolite irreversibly blocks the $P2Y_{12}$ component of ADP receptors on the platelet, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet activation and aggregation

Ticagrelor (Brilinta)

Mechanism of Action

Reversibly and noncompetitively binds the adenosine diphosphate (ADP) $P2Y_{12}$ receptor on the platelet surface which prevents ADP-mediated activation of the GPIIb/IIIa receptor complex thereby reducing platelet aggregation. Due to the reversible antagonism of the $P2Y_{12}$ receptor, recovery of platelet function is likely to depend on serum concentrations of ticagrelor and its active metabolite.

Antiplatelet Drugs Effect on Bleeding

The most commonly encountered antiplatelet combination is aspirin with clopidogrel (for acute coronary syndrome). Evidence relating to bleeding risks with prasugrel and ticagrelor in the context of dental procedures is very limited.

No suitable test equivalent to INR is available for these drugs. Patients on dual antiplatelet therapies may have a higher risk of prolonged bleeding compared to those on a single antiplatelet drug and should be managed accordingly.

Recommendation

If the patient is taking ASA alone then treatment can be preformed **without** interrupting their medication.

For patients taking dual antiplatelet drugs treatment can be preformed **without** interrupting their medication.

It has been found that because bleeding after dental procedures, including multiple dental extractions can be reduced with local measures during surgery (eg, absorbable gelatin sponge and sutures) and the unlikely occurrence of bleeding once an initial clot has formed; there is little or no indication to interrupt antiplatelet drugs for dental procedures.

Healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation. Such professionals who perform these procedures should contact the patient’s cardiologist if issues regarding the patient’s antiplatelet therapy are unclear, to discuss optimal patient management strategy.

Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of antiplatelet

therapy (12 months after drug eluting stent implantation if they are not at high risk of bleeding and a minimum of 1 month for bare-metal stent implantation).

Novel Oral Anticoagulants

Apixaban (Eliquis)

Mechanism of Action

Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of free and clot-bound factor Xa (FXa). FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin.

Dabigatran (Pradaxa)

Mechanism of Action

Is a prodrug lacking anticoagulant activity that is converted to the active dabigatran, a specific, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI, and XIII, and inhibition of thrombin-induced platelet aggregation

Rivaroxaban (Xarelto)

Mechanism of Action

Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa (FXa) in both the intrinsic and extrinsic coagulation pathways. FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, factor II and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin.

Novel Oral Anticoagulants Effects on Bleeding

The INR test is not suitable for assessing coagulation levels in patients taking dabigatran, apixaban or rivaroxaban. Compared to warfarin, novel oral anticoagulants exhibit a rapid onset of action (2-4 hours) and have relatively short half-lives (5-13 hours for rivaroxaban, ~12 hours for apixaban and ~13 hours for dabigatran, depending on renal function and age). Due to these pharmacokinetic properties, it is possible to modify the patients' anticoagulation status quite rapidly. Therefore, we can minimize the period where anticoagulation activity is sub-optimal. No reversal agents are present currently on the market.

Apixaban (Eliquis) and dabigatran (Pradaxa) are taken twice a day, while rivaroxaban (Xarelto) is most commonly taken once a day, either in the morning or at night. For each of the drugs, a lower dose is indicated for certain patients with renal impairment and elderly patients. Patients with acute deep vein thrombosis or pulmonary embolism may be taking high dose apixaban or rivaroxaban for the first 1 to 3 weeks of treatment. It would be advisable to delay any dental procedures likely to cause bleeding until the patient is taking the standard doses.

Recommendation (assuming a morning appointment)

For patients who are taking **apixaban** or **dabigatran** advise them to **miss** their morning dose and take their evening dose at the usual time, if it is no earlier than 4 hrs after haemostasis has been achieved.

If patients take a morning dose of **rivaroxaban**, advise them to **delay** their medication. The delayed morning dose may be taken 4 hours after haemostasis has been achieved.
The next dose should be taken as usual the following morning.

If patients take an evening dose of **rivaroxaban**, **no modifications are recommended.** They can take the medication at their usual time, on the day of treatment, if it is no earlier than 4 hours after haemostasis has been achieved.

Injectable anticoagulants

These drugs may be administered once or twice a day at either prophylactic or therapeutic doses. These drugs have a short onset of action and short half-lives.

Enoxaparin

Mechanism of Action

Acts as an anticoagulant by enhancing the inhibition rate of clotting proteases by antithrombin III impairing normal hemostasis and inhibition of factor Xa. Low molecular weight heparins have a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa.

Dalteparin

Mechanism of Action

Dalteparin has been shown to inhibit both factor Xa and factor IIa (thrombin), the antithrombotic effect of dalteparin is characterized by a higher ratio of antifactor Xa to antifactor IIa activity (ratio = 4)

Tinzaparin

Mechanism of Action

Tinzaparin is a low molecular weight heparin that binds antithrombin III, enhancing the inhibition of several clotting factors, particularly factor Xa. Tinzaparin anti-Xa activity is greater than anti-IIa activity it has a higher ratio of antifactor Xa to antifactor IIa activity compared to unfractionated heparin

Recommendation

Patients are often given heparin or one of the LMWHs during kidney dialysis. The **dental treatments** likely to cause bleeding should be **delayed until the following day**.

Take Home Message

Don't discontinue anticoagulation or antiplatelet drugs for your patients and work around the dosing schedule, especially when it comes to novel oral anticoagulants. As new drugs continue to flood the market our techniques and protocols will have to evolve with them.

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