Introduction

Two of the most important problems you will face as a doctor are coagulation and bleeding, normally they are in balance, and we need always to keep that balance by either increasing the coagulation or, mostly, decreasing the coagulation that can block blood vessels.

Coagulation can be resulted from certain diseases (like DVT or angina) by producing thrombi that can block substantial arteries like the coronary artery, preventing blood from reaching the heart followed by ischemia.

Atherosclerosis is the common risk factor for coagulation, which is caused by hyperlipidemia (high cholesterol, and lipids are accumulating inside the vessels). This causes degeneration of the walls of the arteries (atheroma) exposing the collagen of the walls to blood, so platelet aggregation occurs forming a plug which can partially or completely close the vessel.

If a plug completely closes a coronary artery it will case myocardial infarction, if it was partially closed it will cause angina pectoris.

Angina pectoris is when supply of oxygen to the heart is not enough (The oxygen supply does not meet the demand) so angina (ذبحة صدرية) occurs. There are two types of angina stable and unstable and we will get to them later.

Sometimes the clot moves in the body and it ends up closing an artery that supplies the brain. This case is called stroke.

Antiplatelets & anticoagulants are two types of drugs we give patients to prevent these former situations from happening. Most of the time (except for some cases) we give these drugs and prophylaxis rather than a treatment because patients don’t feel the coagulation or any pain until the closure happens, so these drugs are mostly used as prophylaxis to prevent coagulation from happening.

Also, we use these drugs for patients who previously had angina or MI, so these patients are highly susceptible for thrombosis.
1) Antiplatelets

For a thrombus to be formed, platelets aggregate, they then crosslink with each other, so coagulation happens. What antiplatelets do is they prevent platelets adhesion to exposed collagen or they prevent platelet aggregating.

Note: if the platelets are already aggregated and cross linked with each other by fibrin (platelet are already coagulated), antiplatelets are useless because aggregation already happened. So, for treatment we don’t use antiplatelets, they are only used as prophylaxis.

2) Anticoagulants

They can sometimes be used as treatment because they prevent the thrombus from getting bigger, and with time it may get smaller. So, anticoagulants are used in prevention and in treatment.

3) Thrombolytic drugs

These drugs are sometimes called (إبرة الحياة) because they dissolve (lyse) the plug or the thrombus. So, for patients who have stroke or MI we give thrombolytic drugs as the best try to save their lives.

Note: Thrombolytic drugs are very hard to deal with because of the unselectively, so they are going to dissolve every thrombus either good or bad (good thrombi prevent us from bleeding).

4) We will also talk about coagulant drugs: they are used usually to facilitate clotting and reduce bleeding, for example in heavy menstruating female, we give drugs to reduce the amount of bleeding. Other example is in dentistry clinics. Dentists have certain type of acidic material to increase the speed of clot formation to stop bleeding.

Coagulation pathway

When damage occurs to the vessel wall endothelium, collagen will be exposed to the blood, and platelets will adhere to the damaged
endothelial this will stimulate the degranulation of the platelets causing the release of cytoplasmic granules’ substances including **thromboxane A2** and ADP. These two will attract more platelets to the injured area, they do this by binding to their specific receptors on the platelets. ADP’s receptors are called **P2Y1**, and thromboxane A2 receptors (TXA2).

*Fibrinogen is produced by the platelets and binds to a receptor on other platelets called **gp2b3a** which also stimulates aggregation.

Prothrombin will be converted to thrombin, then thrombin activate fibrinogen to form fibrin, then fibrin will form the plug.

**The next points are very important, understand them well.**

When plug gets stuck to the coronary artery wall, it may cause **stable** or **unstable angina**. It’s **stable** when the plug is **intact** and does not move. But when the plug burst and rupture it’s now **unstable**, so parts of it start wobbling and moving in and out near the plug (بِتَلْوَلح).

With stable angina patients start feeling the pain only when they exercise (it’s called exercise angina).

But with unstable angina it’s random. The patient may be resting, and he starts feeling pain, what happened is that the plug was moving and then closed the artery, and of course, exercising makes it worse.

**Antiplatelets**

**Aspirin**

Very old drug (first antiplatelet).

- **Mechanism of action:**

Blocks COX 1 & 2. So, it’s **not selective**.

-The doctor mentioned that Celecoxib (Celebrex) is a COX-2 inhibitor. Remember, COX 2 is activated in case of inflammation while COX1 is always active. COX1 is the key enzyme in prostaglandins biosynthesis, which have many important functions in our body including promotion of the production of the natural mucus lining that protects the inner stomach and acts on parietal cells in the stomach wall to inhibit acid secretion so drugs which inhibits COX1 (E.g: Non selective NSAIDs (
Aspirin; Diclofenac; Ibuprofen; Naproxen) will cause **epigastric distress** and thus they are contraindicated in case of peptic ulcer. Celebrex is not because it only acts on COX2.

- Blocking COX 1 will inhibit production of thromboxane A2, as well as prostaglandins and prostacyclin. Also, all NSAIDs function the same way, **but aspirin is the only NSAID that has antiplatelets action**, why?

**Aspirin binds toward COX irreversibly**, eliminating the production of thromboxane A2.

**Other NSAIDs (like Ibuprofen) do not have antiplatelets action, because they bind to COX temporarily then they dissociate, so there is no real action.**

- **Side effects:**
  
  High chance of **bleeding** and **ulceration** that sometimes can be dangerous.

  But why do we take them though?

  **The key for giving aspirin is the dose**, the higher the dose the more side effects including more bleeding and the more effect toward bad coagulation.

  **Luckily, even low doses of aspirin (baby aspirin 81mg) is enough to produce antiplatelets effect only, (no analgesic, anti-inflammatory or antipyretic effect). Higher dose (adult aspirin 325 mg) can produce all the previously mentioned effects, but with high risks of bleeding if daily doses were taken. So, baby aspirin is weak, but enough to prevent platelets aggregation.**

  **Caution: Baby aspirin is not for babies.** We don’t give it to babies because of the risk of **Reye syndrome**. Other than that, they may have allergy toward it (10-15% of children), even some adults have allergy toward aspirin. **So aspirin is contraindicated in children and adults with aspirin allergy.**

- **Uses:**

  As prophylaxis to prevent **myocardial infarction** and **angina pectoris**.
Usually it’s not given alone, we give other medications (like clopidogrel), especially with patient with higher risk to develop infarction or angina, or with patients who have gone through one of these conditions.

**Clopidogrel**

Commercial name is **Plavix**, it’s very widely used in Jordan and worldwide. (Doctor said you should know commercial names especially the famous ones).

It’s useful for patients who can’t have aspirin because of allergy. If there is no allergy, we give aspirin with it (**dual antiplatelet therapy**).

- **Mechanism of action:**
  - block ADP receptors on platelet so it blocks platelet activation and degranulation.

**Uses:**

Used with aspirin normally to prevent vascular events in patients with **Transient Ischemic Attack** (it’s like a stroke, but milder), **Unstable angina**, and prevent **thrombosis stroke**.

**Clopidogrel is also used to prevent thrombosis for patients under coronary stent.**

When a plug is formed, one of the major solutions is to prevent it from closing the vessel by putting a stent (شبكة). Some stents (drug eluting stents) have drugs in them but in very low amount. Usually the drugs used are immunosuppressant “Cyclosporin” or chemotherapy medication “Paclitaxel”.

When the stent is put in the vessel it will injure it, making collagen exposed toward the blood and stimulating platelets. Drug eluting stents have very little amount of certain drugs that will be secreted and kill platelets, but that’s not enough.

The major idea here is that we give clopidogrel before the surgery to prevent platelets aggregation after injuring the vessel.
Another important thing is that if the patient takes high doses of aspirin “Not baby aspirin” (like rheumatoid arthritis patients) we tell them to stop taking aspirin 5-7 days before the surgery (to give platelets a chance to be active and start COX pathway), why do we do that? To prevent uncontrolled bleeding, then we give the patient clopidogrel to have less antiplatelet effect.

**Note:** Why we stop it for 5-7 days before surgery? To give the platelets a chance to recycle, The half-life of circulating platelets is 8 to 9 days, remember that aspirin binds irreversibly to COX, and I want the platelets to be active and have thromboxane A2, so I wait 5-7 days till the platelets which have aspirin bound to their COX enzyme are destroyed and I have new platelets with Aspirin free COX enzyme.

But if the patient is on aspirin 81mg he can take that drug even before the surgery and we give him clopidogrel too also to make more antiplatelets effect.

How do we give it? We give a **loading dose** right before the surgery (4 tablets orally of 75mg=300mg), and after surgery we give 1 tablet every day.

**Some patients even though we give them clopidogrel, they have clotting on the stent. It’s because they have genetic problem. You should know that clopidogrel is a pro-drug, it needs **CYP2C19** enzyme to be activated. If the patient has deficiency or absence in that enzyme clopidogrel won’t perform its function.

How long do we give the patient clopidogrel after stent surgery?

- In low risk patients: for 1 year, but in real life most of the patients are at high risk to develop thrombosis and myocardial infarction, because they mostly they are obese and have atherosclerosis. So usually we give it to them for lifetime, with aspirin of course. (Although books and guidelines are now saying we give it for 3 years, but the reality is different).

How do me manage this issue? By monitoring the patient, we give them clopidogrel and then we take a blood sample from them and put it in a device called Multiplate analyzer and then we see whether there is
clotting or not if there is clotting then this means that clopidogrel was not activated and there is a problem in CYP2C19. So, we must give the patients another drug called prasugrel.

Note mentioned by the doctor in some cases in deficiency of CYP2C19 when the patients are heterogeneous we give them clopidogrel but instead of 75 mg we give them 150 mg and the loading dose instead of 300 mg we give them 600 mg.

- **Side effects:**

Bleeding, but it rarely occurs with daily dose of 75mg (1-2% of patients).

Note mentioned by the doctor in some cases in deficiency of CYP2C19 when the patients are heterogeneous we give them clopidogrel but instead of 75 mg we give them 150 mg

**Ticlopidine**

Before clopidogrel, P2Y1 inhibitor (ADP receptor).

Still rarely being used, but has many adverse effects: it causes *neutropenia, Thrombotic thrombocytopenic purpura (bleeding under the skin), and bleeding*. Clopidogrel doesn’t have these side effects.

**Prasugrel**

Usually we give it to patients who can’t have clopidogrel (CYP2C19 deficiency).

More rapid onset of action. Achieves higher degrees of platelets inhibition than clopidogrel.

Compared with clopidogrel, 19% reduction of cardiovascular death, Myocardial infarction and strokes when given at time of pre PCI (before Stent).

However, it greatly increases bleeding risks including life threatening bleeding.

It’s contraindicated in patients with history of strokes, age > 75 or weight <= 60g.
**Looking at the side effects, and because of high bleeding risk, don’t ever give Prasugrel to your patient except if they have CYP2C19 deficiency, also give it with aspirin.**

Loading dose is less than clopidogrel (60 mg), and normal dose is also less (10 mg)

**Glycoprotein IIb/IIIa inhibitor (Abciximab)**

Humanized **monoclonal antibody**, directed against IIb/IIIa complex.

**IIb/IIIa is where fibrin binds on platelets to start coagulation. So when we give abciximab, even if clotting occurs, no coagulation will happen.**

**Injectable not orally given.**

Is given to patient who need catheterization immediately (1 hour before).

Fast acting drug, no need for loading dose.

*Please refer to the slides.*

**Quick summary:**

Atherosclerosis, high risk for stroke, MI or angina: Aspirin and clopidogrel.

Aspirin is the only NSAID that have antiplatelet action.

Aspirin stops thromboxane A2 production.

Aspirin allergy: only clopidogrel

Before coronary stent procedure:

1- If the patient has high aspirin dose → stop it and give him clopidogrel
2- If the patient has low dose aspirin → add clopidogrel.
3- Loading dose of clopidogrel before procedure.

Clopidogrel stops degranulation and ADP secretion → no aggregation.

CYP2C19 → Prasugrel

Prasugrel has better effect, but more bleeding
Ticlopidine side effects: TTP, neutropenia and bleeding

Abciximab is injectable, and given right before catheterization, inhibit IIb/IIIa complex → no coagulation.