Coagulation Abnormalities Made Easy

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Back decades ago, the coagulation cascade was taught in terms of 2 pathways, the intrinsic versus the extrinsic. Figure 1 shows a very simplified version of the proposed waterfall/cascade model of the coagulation system. Unfortunately, as we started to understand more about the coagulation system, it became more and more complex. Many of the enzymes were found to be cofactors or were precursors to the active form. We also found that the 2 pathways were not completely separate in function. They appeared to be an intertwined system where modulation of one arm may or may not affect the second arm. The modern view of coagulation is to actually look at the coagulation system as a series of steps, 1) initiation, 2) amplification, and 3) propagation, as opposed to distinct pathways, (1) but the old 2 pathway model is still beneficial in terms of helping us understand what abnormal coagulation tests mean. This chapter will exam some causes of abnormal coagulation in the perioperative period and discuss agents that are used to modulate the coagulation system.

**Intrinsic Pathway (aPTT)**

Kallikrein → fXII → fXI → fIX → fVII → fX

**Extrinsic Pathway (PT)**

Tissue Factor → fVII → fX → fII

**Common Pathway**

Fibrin

Figure 1: Waterfall/Cascade Model of the Coagulation System

Pre-operative causes of abnormal coagulation

Most patients with congenital coagulation abnormalities present in early life and come to surgery with a known diagnosis. Patients with hemophilia, von Willebrand disease (vWD), and platelet disorders usually need treatment before, during, and after surgery. For the patient without a diagnosis of a prior coagulation abnormality, the best
means of detecting a hemorrhagic diathesis is a properly taken history. Some screening pre-operative questions that may help flush out a bleeding history are:

1) Is there a history of bleeding in the family?
2) Is there a history of bleeding after procedures (such as biopsy, tooth extraction, surgery)?
3) Do you experience recurrent nosebleeds?
4) Do you experience recurrent gum bleeding?
5) Do you experience bruising routinely?
6) And for females, do you have heavy periods (10 pads/d x 4 days)?

Equally important is a detailed history of drug ingestion and herbal remedy use.

Pre-op abnormalities are best classified based on the abnormal laboratory value – platelet count, fibrinogen level, prothrombin time (PT) or activated partial thromboplastin time (aPTT). PT abnormalities are associated with deficiencies or inhibitors of FII, FV, FVII, FX, or fibrinogen, which are often associated with liver disease, vitamin K deficiency, or warfarin effect. Activated PTT abnormalities can be associated with deficiencies or inhibitors of FII, FV, FVIII, FIX, FX, FXI, FXII or fibrinogen. Diseases often associated with these deficiencies include: hemophilia A (VIII), hemophilia B (IX), lupus anti-coagulant, and heparin or thrombin inhibitor effect.

An algorithm for further pre-operative work-up for an abnormal PT or aPTT and a positive bleeding history is shown in figure 2. Patients with a positive bleeding history, but normal PT and aPTT, should be sent for hematology consultation for more extensive work-up. In this instance, low or dysfunctional platelets, mild deficiency of von Willebrand factor, vascular disorders, and, rarely, factor XIII deficiency should be considered.
Figure 2: Algorithm for work-up of an abnormal pre-operative PT or aPTT

Intra-operative causes of abnormal coagulation

There are really only 2 main causes of perioperative bleeding. The first and most common is surgical bleeding, which will not be discussed here. The second is non-surgical bleeding, or failure of the hemostatic pathways. Causes for this failure include: massive blood transfusion (leading to thrombocytopenia, low fibrinogen, and coagulopathy), fibrinolysis (induced by the surgical procedure such as prostatectomy, orthotopic liver transplant, or exposure to a foreign graft material), disseminated intravascular coagulation (from sepsis, cardiopulmonary bypass, or transfusion reactions), an undetected pre-existing bleeding disorder or a combination of the above possibilities.

The mainstays of massive blood loss management basically include replacement of red cells, platelets, clotting factors and fibrinogen. The patient needs to be kept warm and frequent labs are necessary to help guide transfusions and electrolyte replacements. A basic laboratory profile in the operating room should include hematocrit, platelet count, PT, aPTT, and fibrinogen level. Antifibrinolytics like tranexamic acid and epsilon-aminocaproic acid can be given if fibrinogen levels remain low and a mechanism for primary fibrinolysis seems likely. Disseminated intravascular coagulation (DIC) is difficult to diagnose during surgery since there is no one pathognomonic laboratory test. Surgical bleeding alone can cause an elevated PT, low fibrinogen levels, and low platelet count. Distinguishing between primary fibrinolysis and DIC by laboratory values intra-operatively is also very difficult. The diagnosis may sometimes have to depend on the clinical scenario. D-dimers can be sent, but the results will not be available quickly. The first goal for treatment of DIC is to correct the primary disorder if possible and then replace fibrinogen, platelets, and coagulation factors as necessary. In some patients, the correction of the primary disorder may not be readily possible. Heparin therapy is not universally accepted in the treatment of DIC, and the decision to use heparin, especially intra-operatively, should be discussed with the surgical team and the hematologists.

Recombinant factor VIIa (rFVIIa)

One drug that may help during massive hemorrhage is recombinant factor VIIa. A growing number of case reports suggest that this agent may be effective in various “off-label” indications. It has been used in controlling intractable bleeding in trauma, obstetrical, and surgical patients where all other efforts to correct the bleeding have failed to work. Because this drug has seemed to be the magical pill, its use has progressed from rescue therapy to preventative therapy in surgical situations such as complex cardiac surgery or liver transplantation where heavy blood loss is expected. When rFVIIa is administered, hemostasis is enhanced because of the additional generation of thrombin. In the tissue factor dependent or extrinsic system, rFVIIa binds to tissue factor at the site of vessel injury, causing activation of factor X. In the tissue factor independent or intrinsic system, rFVIIa binds to the surface of the activated platelet, activating factor X. Both mechanisms result in a “burst” of thrombin and fibrin generation, which leads to clot formation (Figure 3).
In a randomized controlled trial conducted in 36 patients undergoing radical prostatectomy, patients were randomized to placebo, rFVIIa at 20 mcg/kg or 40 mcg/kg. (2) Patients receiving rFVIIa had a mean blood loss that was statistically significantly lower than the control group. In trauma patients, the use of rFVIIa reduced the need for massive blood transfusions (defined as > 20 units) from 33% in the control group down to 14% in the treatment group. (3) While the results for penetrating trauma are just as promising, the results did not reach statistical significance.

During orthotopic liver transplant (OLT), where there is dilution of coagulation factors and platelets, level 3 or 4 evidence (ie case reports) have been published, but no randomized controlled trials. A few reported studies have actually been unable to show decreased transfusion requirements with the prophylactic use of rFVIIa in OLT. There are several reasons why rFVIIa may not work as well during OLT. 1) Recombinant FVIIa has no effect against heparin or heparin-like substances, which may have been released by the reperfused liver. 2) Recombinant FVIIa has no direct anti-fibrinolytic effect. Anti-fibrinolytics may be necessary since fibrinolysis may occur after reperfusion. 3) Because of the fibrinolysis and low fibrinogen levels, rFVIIa may not be as effective. FFP or cryoprecipitate may still be required since fibrinogen is required for the thrombin burst to produce the fibrin clot.

In all, 2 meta-analyses and 1 Cochrane report have been published. (4-6) Depending on the inclusion criteria, most included only 7 to 13 trials. Approximately 700 patients have been enrolled in trials involving the prophylactic use of rFVIIa during OLT, liver resection, prostatectomy, repair of pelvic trauma, and cardiac surgery. Approximately 1200 patients have been enrolled in the therapeutic use of rFVIIa. The underlying etiologies for the use of rFVIIa have been quite varied, and include stem-cell transplant, dengue fever, trauma, upper GI bleeding, and intracranial

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**Figure 3: Mechanism of action of rFVIIa**

[Diagram showing the intrinsic and extrinsic pathways of blood clotting, including FVIIa, fibrinogen, and clot formation.]
hemorrhage. If all trials are analyzed together, there is a slight reduction in the number of patients that need PRBC transfusions with the prophylactic use of rFVIIa. The effect is mostly from the use of high dose rFVIIa (>50 mcg/kg) and not low dose. In the studies that looked at the use of rFVIIa therapeutically, there is no statistically significant difference between the 2 groups in terms of the number of patients that needed a blood transfusion.

One other end-point of interest other than PRBC transfusions is mortality. The question is: can the use of rFVIIa improve mortality? With only 14 deaths out of 507 patients, the results give a wide confidence interval that crosses 1, so mortality does not seem to be improved from the meta-analyses.

As the use of rFVIIa increases, there are now more reports of thrombosis. O’Connell et. al. look at the FDA adverse event database, which is a voluntary reporting system. Pooling all reported cases in which rFVIIa was used in non-hemophiliac patients resulted in 168 cases of thrombosis attributable to the drug. The rate of complication is uncertain because no one really knows what the denominator is. (7) Patients with procoagulant diseases (cancer, infections, h/o thromboembolic events, and receiving procoagulant drugs) were usually excluded from the studies, so the real risk of thromboembolic events may be much higher when we start using the drug more in the general surgical population or in critically ill patients.

As researchers gain experience with the use of rFVIIa in intracranial hemorrhages, the data show that the drug decreases the size of the hemorrhage, but increases the incidence of thrombosis to 7%. (8) The study was repeated in a phase 3 trial. (9) There was decreased growth in the volume of the intracranial hemorrhage, but there was no significant difference among the groups in terms of mortality. Also, the incidence of severe disability was not improved in the treatment groups. In the second study, frequency of venous complications were the same in the groups, but there remained an increase frequency of arterial events, defined as myocardial infarctions and cerebrovascular accidents, in the rFVIIa group that received the higher dose of 80 mcg/kg.

At this point, the data does not favor the prophylactic use of rFVIIa, but also can’t show definitive harm from its use. Considering that no RCT has been able to demonstrate a significant benefit in terms of ICU stay, hospital stay or mortality, the financial burden of this drug needs to be weighed against the cost benefit of transfusing fewer products. Each clinician will have to weigh the risk of thromboembolic events against the benefit of clotting for the individual patient. More randomized controlled trials are necessary before a definitive statement can be made about the safety of rFVIIa.

**Post-operative causes of abnormal coagulation**

In the post-operative period, usually the deficiency of clotting factors, platelets, and red cells begin to resolve unless there is ongoing surgical blood loss. Now, the imbalance of procoagulant and anticoagulant agents increases the risk for prothrombotic complications. Standard of care is to institute thromboembolic prophylaxis in surgical patients (Figure 4). Heparin is usually the drug that comes to mind, but heparin does have its drawbacks. There is wide inter-individual variability when administering the drug. It is an indirect thrombin inhibitor and therefore, is effective on free thrombin only, and has limited inhibition of clot bound thrombin. It requires anti-thrombin as a cofactor, and it induces platelet activation. The most devastating side effect of heparin is its ability to form a complex with PF4 (platelet factor 4) that then can generate formation of heparin/PF4 antibodies.
Figure 4: Site of action of anticoagulants

**Direct Thrombin Inhibitors**

Direct thrombin inhibitors (DTI), initially isolated from the saliva of leeches, have been developed for use as anticoagulants in patients with HIT. There are now lots of direct thrombin inhibitors on the market that an anesthesiologist needs to be familiar with (Table 1). Most direct thrombin inhibitors are relatively short acting, inhibit free and clot-bound thrombin, and are indicated for prophylaxis and treatment of patients with HIT. One DTI, melagatran, and its oral formulation, ximelagatran, were removed from the market due to hepatotoxicity. The drawback for these drugs is that there are no specific reversal agents. Dialysis may be somewhat effective, and rFVIIa has shown some efficacy in animals and in healthy volunteers ex vivo. (10)

**Table 1: Direct Thrombin Inhibitors**

- Hirudin
- Lepirudin
- Desirudin
- Argatroban
- Bivalirudin
- Ximelagatran/melagatran
- Dabigatran

**Argatroban**

Argatroban has a 45-minute half-life, and it is cleared by the liver, so no dose adjustments are needed in patients with low glomerular filtration rate (GFR). It is less immunogenic than lepirudin, but it does increase the international normalized ratio (INR), which may be a factor when initiating coumadin. Like all direct thrombin inhibitors, it is cleared by the liver. (10)
inhibitors, dose should be titrated to aPTT (1.5-3x normal) or activated clotting time (ACT). The FDA approved this drug as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT and for percutaneous coronary intervention (PCI) in patients with or at risk for HIT. Two prospective, multi-center trials studied 754 patients with HIT versus 193 historical controls. They found a significant decrease in the primary endpoint of death, amputation, and new thrombosis (34% vs. 43%). (11, 12) Safety trials for patients with HIT undergoing PCI showed that argatroban was as safe in terms of procedural success (lack of death, need for emergent CABG, or increased incidence of Q-wave MI) as historical controls receiving heparin (98.2% vs. 94.3%). There are also a few reports of the successful use of argatroban in ischemic stroke, hemodialysis, CRRT, and peripheral vascular surgery.

**Bivalirudin**

Bivalirudin has a 25-minute half-life, and it is 80% cleared by proteolysis and 20% renally cleared. Unlike argatroban, it needs to be dosed for GFR, and it only causes a slight increase in INR. The dose should be titrated to aPTT (1.5-3x normal) or ACT. The FDA approved this drug as an anticoagulant for PTCA in patients with unstable angina (13) and for PCI. Multiple RCTs have studied the use of bivalirudin for PCI versus heparin. (14, 15) Most show similar ischemic outcomes in both groups with less major bleeding in the bivalirudin group. Other studied uses of bivalirudin include cardiopulmonary bypass and vascular surgery. Table 2 summarizes a comparison between the different direct thrombin inhibitors.

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<th>Lepirudin</th>
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<th>Bivalirudin</th>
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**New Oral DTI – Dabigatran**

The US FDA recently (October, 2010) approved dabigatran, an oral direct thrombin inhibitor, for the management of patients with atrial fibrillation. Because of its predictable pharmacokinetics and few drug or food interactions, dagibatran can be given as a fixed daily dose without the need for coagulation monitoring. The new oral DTIs show promise in reducing the complexity of current anticoagulants. (16)

**Fondaparinux**

One new anticoagulant is fondaparinux, a synthetic five saccharide molecule that is functionally and structurally like heparin. It binds and activates antithrombin, but unlike heparin, it only inhibits FXa and not thrombin. The drug has not been extensively studied for HIT, but successful use of fondaparinux in patients with HIT has been reported. One multicenter in vitro study demonstrated a lack of cross-reactivity between fondaparinux and HIT antibodies. (17) Recently, 2 case reports of thrombocytopenia without thromboembolic complications while receiving fondaparinux have been described. (18, 19) At this time, the American College of Chest Physicians continues to recommend the use of direct thrombin inhibitors as the first-line agents in the setting of HIT. (20) Further clinical trials should be conducted before fondaparinux becomes the therapy of choice for HIT.
Rivaroxaban

Direct Xa inhibitors are new agents whose activity is directed against the active site of Factor Xa. These agents are being investigated for use in prophylaxis of DVT, PE, and stroke in patients with atrial fibrillation. Like dabigatran, these agents also have minimal drug interactions and predictable pharmacokinetics. For the majority of patients, coagulation monitoring is unnecessary.

Use with Regional Anesthesia

There is not a lot of data on the use of these new anticoagulants with regional anesthesia. The broad clinical experience with these drugs and neuraxial techniques does not exist. Most recommendations are based exclusively on the pharmacokinetics. (21)

Drug Reversal

A major disadvantage of the new oral anticoagulants is the lack of a reversal agent in case of serious bleeding. One study looked at 12 healthy male volunteers in a cross-over study. They received rivaroxaban or dabigatran followed by a bolus of a prothrombin complex concentrate (PCC). Laboratory values were then followed. It appears that the PCC was able to reverse the laboratory anticoagulant effect of rivaroxaban but not dabigatran. Of course, it is unclear whether the chosen laboratory values are good surrogate markers for the actual clinical bleeding potential. More studies are clearly needed. (22)

Given the lack of data, current recommendations in the face of serious bleeding are to provide support care with fluid resuscitation, site compression, and transfusion, discontinue the drug, consider activated charcoal for recent ingestions, and possibly start hemodialysis for dabigatran. (23) There is not enough data to make recommendations about FFP, PCC, and rFVIIa.

Summary

The modern view of coagulation is of a highly complex system with multiple cofactors and enzymes divided into the initiation, amplification, and propagation phase of clot formation. The older view of an intrinsic and extrinsic pathway, although greatly simplified, is still useful because it illustrates what the coagulation tests are measuring. Analyzing the PT or aPTT can help diagnose the coagulation defect. Bleeding diatheses in the perioperative period are easier to discuss when we divide the differential into the pre-, intra-, or post-op periods. Several new drugs that either increase clotting or increase anticoagulation have been introduced, and many more are due on the market. It is the anesthesiologist’s job to understand their mechanisms of action, how to manipulate the drugs in the perioperative period, and how the drugs will affect the anesthetic plan.

References

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