Clinical aspects of coagulation and haemorrhage

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Abstract

Haemorrhage affects all patient groups. Coagulopathy (an abnormality of the clotting system) is closely interlinked with haemorrhage and can either place patients at risk of future bleeding or can exacerbate active ongoing bleeding. There are many causes of coagulopathy, both inherited and acquired. During major haemorrhage, the presence of an acquired coagulopathy increases the likelihood of a poor clinical outcome and a patient is more likely to require large transfusion volumes, critical care admission and is three to four times more likely to die. Other forms of coagulopathy, such as drug-induced coagulopathy (anticoagulant/anti-platelet use) or inherited bleeding disorders, both increase the severity of any active bleeding and also place patients at higher risk for future bleeding when exposed to a haemostatic challenge, such as surgery. This risk must be recognized and mitigated. This review focuses on the clinical aspects of coagulation and haemorrhage in all these patient groups.

Keywords Anticoagulants; coagulopathy; fibrinolysis; inherited bleeding disorders; major haemorrhage; tranexamic acid; transfusion

Royal College of Anaesthetists CPD Matrix: 1A01, 2A05

Learning objectives

After reading this article, you should be able to:

- understand the broad coagulation changes that occur with acquired major bleeding and define the major differences between trauma and postpartum haemorrhage
- recognize the pros and cons of using standard laboratory tests or viscoelastic tests for prediction and treatment of acquired coagulopathy
- manage anticoagulants in an emergency as well as perioperative settings
- define the important steps in the management of a patient with an inherited bleeding disorder in the perioperative setting

Haemorrhage and its consequences are an important cause of morbidity and mortality across all specialty groups. Broadly speaking, patients affected by bleeding fall into two distinct groups: those with major haemorrhage, where management focuses on immediate, emergency therapy to 'stop the bleeding', and then a much larger group of patients who do not have active bleeding but rather are at increased risk of bleeding (e.g. due to use of anticoagulant/antiplatelet medication or an inherited bleeding disorder). The management of this second group focuses on recognition of their bleeding risk and implementation of strategies to mitigate blood loss.

Coagulation and bleeding are intrinsically linked and coagulopathy whether it is inherited, acquired, or drug induced has the potential to exacerbate haemorrhage. The aims of this review are threefold: (1) to describe the coagulopathy of major haemorrhage and the diagnostic strategies available to recognize coagulopathy early and to guide acute haemostatic therapy; (2) to describe optimal management of patients taking anticoagulants and antiplatelet agents, both in the acute bleed setting and the elective perioperative setting; and (3) to discuss the assessment and management of patients with the more commonly encountered inherited bleeding disorders (IBD), such as von Willebrand's disease and haemophilia.

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Major haemorrhage

Major haemorrhage is a leading cause of morbidity and mortality. It is the leading cause of death globally for women in the postpartum period. The economic burden to healthcare systems is high — in 2012, it was estimated that the annual cost of treating trauma patients in England for major haemorrhage alone was £148m. Major haemorrhage is an acute, unpredictable event and management focuses on coordinated timely therapy to treat the bleeding. An important part of this strategy is the rapid diagnosis and subsequent correction of concomitant coagulopathy.

Coagulopathy is known to be associated with poorer outcomes in patients with major bleeding. In trauma, for example, a prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) is associated with a three- to four-fold higher mortality rate and is independently associated with increased transfusion requirements, organ injury, septic complications and critical care stays.[1] It is as a direct result of the increased understanding of the coagulopathy of trauma haemorrhage that there has been a sea change in the management of major haemorrhage over the last 15 years.

Coagulopathy of major haemorrhage

In all clinical situations which lead to major haemorrhage there are several causes of worsening coagulation,[2] and these include:

- *Consumption.* Coagulation factors and platelets are consumed during the formation of clots. This happens in an attempt to prevent loss of blood through damaged vessels.
- *Dilution.* This is a consequence of replacement of the whole blood that is lost with fluids that do not contain plasma, e.g. crystalloid, colloid and red cell transfusion. Coagulation factors are therefore 'diluted' and the levels of clotting factors fall rapidly. High ratio fresh frozen plasma (FFP): red blood cell (RBC) therapy addresses this effect.

- *Hormonal and cytokine induced changes.* Following tissue injury, hormone levels, i.e. adrenaline and vasopressin rise and there is an increase in cytokines. The net result is endothelial cell activation and this leads to a shift in the normal balance of pro- and anticoagulant clotting factors, initially favouring a hypocoagulable (bleeding) phenotype and which over time, as endothelial cell activation continues (due to persistent hypotension, hypoxia and thrombin generation), shifts again to a prothrombotic state. This explains the strong association between significant bleeding and subsequent development of venous thromboembolism.
- *Hypoxia, acidosis, hypothermia.* This triad predisposes to further bleeding. Hypothermia and acidosis impair the functional ability of both the platelets and coagulation proteases. Haemostatic defects are most evident once the pH falls below 7.1 and body temperature falls below 33°C.
- *Ongoing bleeding.* Anaemia has a major effect on primary haemostasis. A low haematocrit reduces axial flow (normally the red cells flow in the middle of a vessel and platelets are pushed towards the endothelium). An inverse relationship has been demonstrated between the haematocrit and *in vitro* bleeding time. (The bleeding time is a test no longer used in haematology but which evaluated primary haemostasis i.e. the haemostatic capacity of platelets and von Willebrand factor).

Trauma coagulopathy

In addition to the clotting changes that accompany all forms of major bleeding, there are changes that are thought to be specific to certain patient groups. Trauma induced coagulopathy (TIC) is, at present, the most thoroughly understood. TIC is more common in patients with shock and hypoperfusion in combination with moderate to severe injury. The central change that occurs in TIC is activation of protein C driven by high thrombin generation. Accompanying the increased activated protein C (APC) levels are two other important clotting changes: (1) excessive fibrinolysis (APC inhibits plasminogen activator−1 (PAI-1)) and (2) a low fibrinogen level (likely due to a combination of consumption, fibrinogenolysis, fibrinolysis and reduced production).

The importance of fibrinolysis (which causes rapid clot breakdown) in TIC has been known for several years and was confirmed by the CRASH-2 study. This randomized controlled trial (RCT) of over 20,000 trauma patients reported reduced mortality from all causes and from bleeding in the active arm where participants received tranexamic acid (TXA). Survival was most improved in those who received TXA early, within 3 hours of injury.

Postpartum coagulopathy

Other patient groups with major haemorrhage have not been as extensively evaluated. For this reason, it is important to recognize that transfusion strategies such as empiric high ratio FFP:RBC which have been shown to benefit trauma patients may not be the optimal therapy for other patient groups. More research is required to unpick differences (or indeed similarities) between patient groups.

The clotting physiology of pregnant women at term differs from that of other adults − with a shift towards a prothrombotic state. Thrombin generation rises markedly throughout gestation secondary to the increase in nearly all of the coagulation proteases (except factors V, XI and XIII) and the concomitant reduction of anti-coagulants such as protein S. Fibrinogen, von Willebrand factor and FVIII levels rise the most, with the latter contributing to the acquired activated protein C resistance and the shortened aPTT seen by term. The average fibrinogen level by the end of pregnancy is 4−6 g/L (normal range for adults: 2−4 g/L) and for this reason viscoelastic tests (such as TEG or ROTEM) show a global increase in clot strength parameters. It is important to recognize this difference − since a normal viscoelastic trace at term will be markedly different from a normal trace for a non-pregnant patient.

During post-partum haemorrhage (PPH), one of the most important changes to recognize is the presence (or absence) of a low fibrinogen. Unlike trauma, where patients with severe bleeding tend to have a fibrinogen level of approximately 1.5−1.9 g/L, post-partum patients with bleeding appear to divide themselves into two groups (normal fibrinogen and markedly low fibrinogen).[3] This dichotomy is entirely dependent on the clinical cause for the bleeding − for example, placental abruption, DIC and amniotic fluid embolus cause rapid hypofibrinogenaemia, whereas vaginal trauma or uterine atony does not.

Fibrinolysis is another important cause of coagulation disturbance in PPH. The WOMAN trial reported on just over 18,000 women randomized to receive TXA or placebo during PPH. Similar to the CRASH-2 trial, this study reported a reduction in mortality from bleeding in the TXA arm, with most benefit seen early (within 3 hours of bleed onset).

Predicting major haemorrhage

Diagnosis of major bleeding is difficult and is often made using clinical measures (e.g. rising heart rate, falling blood pressure) but these measures can be insensitive, particularly in younger patients in whom blood loss can be masked and haemodynamic stability preserved. Detection and correction of coagulopathy therefore is an important aspect of management of severe haemorrhage. British Society for Haematology (BSH) guidelines recommend the use of serial standard laboratory tests (SLTs) taken every 30−60 minutes to monitor major haemorrhage. European trauma guidelines recommend viscoelastic haemostatic assay (VHA) testing, i.e. TEG and ROTEM.

PT and aPTT: Although prolonged PT and aPTT results are clearly associated with poorer clinical outcomes in major bleeding these tests are poor predictors of transfusion requirement across all specialty groups. For example, in a cohort of 300 trauma patients 60% of those requiring massive transfusion had a normal PTr (prothrombin time ratio). Therefore, the ability of SLTs to guide pre-emptive treatment is limited. However, the value of these tests is still evident when used as a repeated measurement to show serial trends in coagulopathy.

Fibrinogen is a better predictor of bleeding in PPH than PT/aPTT in the early stages of bleed onset. A large observational study showed that a fibrinogen level of $\leq$2 g/L gave a 100% positive predictive value for severe (vs. non-severe) PPH, and for each 1 g/L decrease in fibrinogen the risk for severe PPH increased by

2.63-fold.[4] In trauma, patients with severe bleeding do have lower fibrinogen levels than their non-bleeding counterparts, however, there is not such a clear predictive effect for bleeding.

VHA tests: VHA have also not been shown to be able to predict future bleeding if a test is taken before bleeding starts in an at risk patient.[5] However, in both PPH and trauma, low clot strength measures (and in trauma an increased TEG lysis of ≥3%) indicate that a patient is at higher risk of bleeding. An EXTEM measure at 5 minutes (EXTEM CA5) of ≤35 mm has been shown to be more sensitive than a PTr of ≥1.2 for predicting the need for massive transfusion in trauma. The advantage of many of the VHA measures over SLTs is speed of results and that they can be undertaken near to the patient—the devices can provide clinically useful clot strength measures at 5 and 10 minutes from test start. Similarly to SLTs, serial measurements hold more clinical value than standalone tests.

Treating coagulopathy during major haemorrhage

The aim of treatment for major haemorrhage is to stop the bleeding. Although coagulopathy confers a negative impact on outcomes during bleeding, the inverse — i.e. full reversal of coagulopathy by normalizing PT and aPTT — has not been shown to improve outcomes, and therefore is not the primary goal.

SLT thresholds for transfusion treatment are generally based on historical, not evidence based, strategies — i.e. 'give FFP when the PTr is ≥1.5 xULN' or 'give cryoprecipitate when the fibrinogen is ≤1.0 g/L'. These thresholds have been challenged recently and certainly for trauma haemorrhage empiric transfusion therapy, which does not rely on SLTs, is standard of care and outcomes have improved.

VHA guided transfusion therapy for major bleeding is often used but, outside the cardiac surgery setting, there is currently insufficient evidence for NICE to support their use. However, RCT data are emerging which provide support for the use of VHA-guided transfusion thresholds. In an RCT of women with moderate to severe PPH, a FIBTEM A5 >12 mm indicated a fibrinogen level that was adequate for haemostasis and no supplementation was needed. In trauma, one RCT using rapid-TEG reported a significant reduction in death at 28 days when using VHA-guided transfusion (compared to SLTs), and numbers of haemorrhagic deaths were halved. A second trauma RCT used dual ROTEM measures (FIBTEM A10 >8 mm, EXTEM CT <78 s) as thresholds for transfusion treatment. The authors reported an association between cessation of clinically relevant bleeding and these ROTEM thresholds, suggesting that they could be used as a threshold to withhold transfusion.

There are, however, no definitive high-quality data showing that VHA are more effective than SLTs in most settings of major haemorrhage yet. In trauma a large multi-centre RCT (iTACTIC) comparing clinical outcomes in patients treated using VHA- and SLT-guided transfusion algorithms is due to be completed in 2018 and results are awaited (NCT02593877).

In summary, most clotting tests, whether they are SLT or VHA based, are poor predictors of future bleeding in at-risk patients. Both tests are most useful when taken multiple times and compared serially. If VHA tests are used in your hospital, they should be used within a well-tested and validated transfusion algorithm. Transfusion therapy should continue to be given according to algorithms until bleeding has stopped. Once haemostasis has been achieved, transfusion therapy should not be used simply to correct deranged clotting test results.

Anticoagulants and antiplatelets

Anticoagulation is a risk for major bleeding. Up to 1.25 million people in the UK take anticoagulation, most commonly for stroke prevention, although numbers of younger patients are increasing due to the better safety profile of direct oral anticoagulants (DOACs) and their use as secondary prevention for venous thromboembolism (VTE).

Vitamin K antagonists (VKA)

Warfarin is the most commonly used VKA in the UK. It acts by inhibiting the vitamin K dependent production of several clotting factors (namely factors II, VII, IX, X as well as proteins C, S and Z). Warfarin is measured using the PT and the result is standardized by the INR. There is a strong correlation between INR and bleeding (or thrombotic) risk. The therapeutic window for warfarin is narrow and regular monitoring is necessary. The half-life of warfarin is approximately 36 hours which means that the effects of warfarin will be seen generally for about 5 days after the last dose is taken.

When faced with a patient with critical bleeding who is known to be taking warfarin, it is important to reverse the anticoagulant effect rapidly. Outcomes for trauma patients are known to be worse in patients taking warfarin. Reversal of warfarin should be conducted using combined therapy, namely vitamin K and prothrombin complex concentrate (PCC). PCC immediately replaces the missing/low clotting facto; however, the clotting factors in PCC have a shorter half-life than the effects of the warfarin and intravenous vitamin K must also be given. Intravenous vitamin K has its peak effect approximately 6 hours after administration, just at the point when PCC is beginning to lose its effect.

How to reverse warfarin

Patients with major bleeding on warfarin need reversal of the anticoagulant effect, regardless of INR. Vitamin K can be given at a dose of 5—10 mg IV and the PCC dose should be rounded to the nearest complete vial. For ease, at our hospital we offer weight band dosing: patients weighing <60 kg get 1500 units PCC; 60—75 kg require 2000 units; 76—90 kg require 2500 units and those >90 kg require 3000 units. The dose of PCC is capped at 3000 units. The INR should be rechecked immediately after administration of PCC and again at 6 hours.

In patients with non-major bleeding events, reversal of warfarin often requires vitamin K only and dose depends on the patient's INR. For an INR of ≥5, warfarin should be omitted and 1—3 mg i.v. vitamin K given. For an INR <5, consider i.v. vitamin K 1—3 mg (depending on clinical situation) and modify the warfarin dose. INR needs to be rechecked in 6 hours after administration of intravenous vitamin K.

Perioperative management of warfarin

Perioperative anticoagulation management depends on the balance between bleeding and thrombosis and largely depends on the bleeding risk of the procedure and the thrombotic risk of the patient.

For elective surgery, warfarin should be held for 5 days if reversal of anticoagulation is needed. INR should be repeated the day before surgery and vitamin K given if the INR is $\geq$1.5. A further INR needs to be repeated on the morning of the surgery in these instances. Warfarin can be restarted on the day or one day post operation with the patient's normal maintenance dose if haemostasis is secured.

Bridging with full treatment dose heparin is really only required in patients with high thrombotic risk (consider the following patient groups for this: VTE within previous 3 months or a complex VTE patient with a high target INR; recent stroke/TIA within previous 3 months or multiple risks and AF; or mechanical heart valve). Patients who require bridging with treatment dose heparin usually start LMWH on the morning of day 3 of surgery and LMWH is continued until 24 hours before surgery. Full dose anticoagulation should be withheld for the first 24 hours in low bleeding risk surgery and 48 hours in a high bleeding risk surgery. Do use prophylactic doses of LMWH both for prevention of hospital acquired thrombosis and reducing the patient's overall thrombotic risk, according to your local hospital policy.

Direct oral anticoagulants (DOACs)

DOACs that are currently used in clinical practice include anti-Xa drugs such as apixaban, rivaroxaban and edoxaban; and the direct anti-thrombin agent, dabigatran. In patients experiencing major bleeding or life-threatening bleeding while taking a DOAC the following management is advised. Stop the DOAC. Manage the bleeding according to your local major haemorrhage policy, including the use of tranexamic acid. Take a full coagulation screen including PT, aPTT, fibrinogen, and thrombin time. A drug-specific test can also be taken (i.e. a 'rivaroxaban level'), although not all hospitals are able to offer this service. Do remember that a patient can have significant anticoagulant on board and have normal clotting screens, especially apixaban. Standard ROTEM tests (EXTEM/INTEM CT) can detect DOACs (dabigatran, edoxaban, rivaroxaban) at therapeutic levels, but appear insensitive to apixaban.[5]

Bleeding secondary to dabigatran can be reversed with idarucizumab (a direct anti-dabigatran monoclonal antibody that binds and clears dabigatran). Idarucizumab is given as two 2.5 g IV slow bolus injections. There are no licensed antidotes for the anti-Xa DOACs at present, although andexanet has approval by the FDA and is likely to be available in the UK soon. Treatment of a patient with significant bleeding who is taking an anti-Xa DOAC is more complex due to the lack of a direct antidote. Current practice in the UK includes the use of PCC (50 units/kg) which is given principally to improve thrombin generating capacity. There is no role for intravenous vitamin K in patients with bleeding secondary to DOACs. For non-major bleeding, delay the next dose of a DOAC or discontinue treatment according to the clinical situation. Intravenous or oral tranexamic acid 1 g can be considered.

Perioperative management of DOACs

Due to their short half-lives, bridging with heparin is not used. Discontinuation of DOACs for elective procedures largely depends on a patient's renal function. Dabigatran, apixaban, rivaroxaban and edoxaban should be held 24 hours before low bleeding risk procedures and 48 hours before for high risk-procedures in patients with normal renal function. In patients with poor renal function, the duration of discontinuation of a DOAC will need to be increased. DOACs can be restarted 6–12 hours after very low bleeding risk procedures and 24 hours after low bleeding risk procedures, if haemostasis is secured. For high-risk bleeding procedures, DOACs should not be restarted until at least 48 hours after the procedure/surgery. Remember, restarting a DOAC means that a patient will be fully anticoagulated within a few hours of administration of the drug. Their use should not be compared to warfarin, where even if this is started on the day of surgery, the INR is not therapeutic until 2–5 days later.

For emergency surgery, whenever possible, aim to delay surgery until plasma levels of DOACs fall. Remember the risk of bleeding perioperatively is dependent on the time since the last DOAC dose was taken, the type of surgery and the patient's renal function. If an anticoagulant effect cannot be ruled out, neuraxial anaesthesia should be avoided. The ability to make predictions regarding haemostasis at surgery in patients taking DOACs is limited by the uncertainty in the concentration of each drug that is associated with haemostatic safety.

Practically, tranexamic acid can be used to reduce bleeding in most surgical cases. In patients taking dabigatran, the thrombin time (TT) is acutely sensitive to presence of drug and if it is normal there is likely to be only very low levels of drug on board. If the TT is prolonged, indicating effects of anticoagulant still present, Idarucizumab can be used as a reversal agent where bleeding risk is significant. In patients taking anti-Xa DOACs who require emergency surgery, PCC may be used, but it must be remembered that this is not a direct antidote and may lead to an increased thrombotic risk. In some low risk surgical procedures, it may be prudent to only use a dose of PCC if the patient shows signs of bleeding perioperatively, rather than using it prophylactically. This decision is usually best made with a haematologist and the operating surgeon.

Anti-platelets

Bleeding on antiplatelet therapy

Bleeding in patients during treatment with aspirin, $P2Y_{12}$ antagonists or GPIIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. Platelet transfusion (two to three adult doses) can be as given for critical bleeding or prevention of bleeding before emergency high-risk surgery. Although desmopressin can shorten bleeding time in patients exposed with antiplatelets such as aspirin and clopidogrel, safety concerns in patients with cardiovascular disease often prevents use.

For urgent surgery that imposes high bleeding risk in patients who have taken antiplatelet agents, preoperative intravenous tranexamic acid should be given. If, despite tranexamic acid, there is excessive perioperative or postoperative bleeding or if the bleeding risk is perceived to be very high, administer two pools of donor platelets as well. This may improve haemostasis if given at least two hours after the last dose of aspirin. For urgent low bleeding risk surgery in patients on antiplatelet therapy, routine platelet transfusion should not be given.

For elective procedures, aspirin generally can be continued for most invasive non-cardiac surgeries including neuraxial anaesthesia. However, if the risk of bleeding is high, aspirin can be withheld from day −3 to +7. In patients on dual anti-platelet

agents, low-risk bleeding procedures may be conducted without interruption of antiplatelet treatment. For high bleeding risk procedures, elective surgery should be deferred. If deferral is not possible, aspirin should be continued and the second antiplatelet, i.e. clopidogrel or ticagrelor should be stopped 5 days prior to surgery (7 days for prasugrel).[6]

Management of patients with inherited bleeding disorders (IBD)

Patients with inherited bleeding disorders are at risk of increased bleeding either during or after surgical procedures, even minor ones. Patients with more severe bleeding disorders will usually have a formal diagnosis of an IBD, for example type 2 and 3 von Willebrand's disease (vWD) and severe/moderate haemophilia. However, some patients do not get diagnosed with milder disease until well into adult life.

Screening for IBD perioperatively

The best way to explore whether a patient might have an IBD preoperatively is to ask them about their personal bleeding history and that of their family. Do take care with younger patients, particularly children and male teenagers/young adults as they are much less likely to have been exposed to prior haemostatic challenges (such as menstruation, surgery or childbirth). If a patient says that they have a bleeding history, then grading the severity is important and a history of: previously needing to seek medical attention for bleeding (i.e. epistaxis that won't stop); iron deficiency; troublesome bleeding at more than one site (i.e. nosebleeds and heavy menstrual bleeding) and needing hospital admission and transfusion are important flags. Haematologists tend to use a scoring system, most commonly the ISTH BAT (International Society for Haemostasis and Thrombosis Bleeding Assessment Tool) and the greater the score, the higher the chance the patient will bleed when challenged. An online version of the score can be accessed here: https://bleedingscore.certe.nl/

Clotting screens

The PT and aPTT are often taken preoperatively. A set of normal clotting screen results should not be taken to mean that the patient does not have a bleeding risk. A good history of personal and/or family history is much more specific and weight should be placed on the patient's history over and above a normal clotting screen.

Haemophilia, which is an X linked disorder, has two forms — haemophilia A and haemophilia B (due to absent or low factor VIII or factor IX respectively). Haemophilia may be severe, moderate or mild depending on the baseline clotting factor level of a patient: severe, <1%; moderate, 1–5%; and mild, >5%. Normal clotting factor levels are 50–150%. In all but the very mildest forms of haemophilia, the aPTT will be proportionately prolonged according to the factor VIII/IX level. However, when a factor level is greater than 30% the aPTT can be within the normal range and the patient may still have very mild haemophilia. In addition to this, some forms of mild haemophilia have a mutation that is not picked up by all clotting assays, such that an aPTT may be normal even when the functioning FVIII level is low. This is known as a one-stage/two-stage clotting factor discrepancy. Here again, the history from the patient is important. Do not forget that carriers for haemophilia may also have a low clotting factor level and may require perioperative haemostatic support.

VWD can be divided into three broad types — 1, 2 and 3. Type 1 is the most common and generally has the mildest phenotype and is due to quantitative reduction of normal VWF. Type 2 comes in four forms and is due to the production of qualitatively abnormal VWF — such that normal amounts of VWF are made, but put simply it doesn't work very well. Type 3 is the most severe form of VWD with levels of VWF (and FVIII) <5%.

In mild VWF and some forms of type 2 VWD, the aPTT can be normal. (Remember — VWF levels don't influence the aPTT, it is the FVIII level that does).

Management

Once the diagnosis of an IBD is recognized, close liaison with the local haemophilia centre is vital. Patients who have a diagnosis of IBD will have a 'haemostasis/bleeding card' and if you ask to see it, it will contain a brief description of their diagnosis, their regular treatment and how to contact their haemophilia centre. Sometimes, patients expect that non-haemophilia doctors should know of their bleeding condition and do not mention it, particularly if being treated in the same hospital. It is always worth asking the question!

In general, most patients with a diagnosis of an IBD will require some form of haemostatic support perioperatively. This varies according to the severity of their condition and the type of surgery required. Haemostatic therapy can broadly be thought of in three steps:

Tranexamic acid inhibits clot breakdown. It is a synthetic analogue of the amino acid lysine and reversibly binds to the lysine receptor sites on plasminogen. This prevents plasminogen from being converted to plasmin, a potent fibrinolytic enzyme. In general, tranexamic acid is a useful medicine for all patients with IBD and can be used alone in minor procedures or in combination with DDAVP or factor concentrate for more significant surgery.

DDAVP: Desmopressin is a synthetic form of vasopressin and works by stimulating the release of VWF from the Weibel—Palade bodies of endothelial cells. VWF levels (and FVIII levels), in those patients who respond to DDAVP, increase by 3–5-fold with the peak level expected 90 minutes after a subcutaneous injection. DDAVP is useful in some forms of VWD and for mild haemophilia. The dose is much higher than the dose given for renal patients — i.e. 0.3 micrograms/kg and a specially formulated DDAVP is used for subcutaneous injection, called Octim.

Clotting factor concentrate: Factor VIII or IX concentrate is given to haemophilia patients perioperatively, when required. In UK, these factor concentrates are now recombinant. However, haemophilia patients were treated in the past with plasma products and some patients will have been exposed to vCJD. The patient's haemophilia centre will hold information about the patient's vCJD status.

VWD is treated, when necessary, with VWF concentrate that contains both VWF and FVIII. This is currently only available as a plasma derived concentrate.

Neuraxial anaesthesia and IBD

In many cases, when a patient is treated perioperatively for their IBD, nerve blocks, epidural or spinal anaesthesia can be used. Care should be paid to the timing of the removal of an epidural – and again close liaison with the haemophilia centre is advised – as factor levels should be greater than 50% for removal. However, for VWD, even when treated with VWF concentrate, the UK haemophilia doctors organization (UKHCDO) advise against neuraxial anaesthesia, particularly for type 2 and 3 VWD patients.[7]

Duration of treatment

Duration of therapy will mostly be dictated by the type of surgery the patients has undergone. Treatment may therefore be a one-off (i.e. dental surgery) or may be required for 2 weeks (i.e. neurosurgery). IBD patients, particularly haemophilia patients, are at increased risk of late bleeding postoperatively. The haemophilia centre will provide a surgical plan and regular input into the patient's care postoperatively.

The management of coagulation abnormalities in the context of bleeding can be challenging. Outside haemophilia and warfarin therapy, where the aPTT and the INR are sensitive diagnostic and therapeutic measures, SLT and VHA tests are generally not good predictive measures for risk of bleeding and should not be relied on. SLT and VHA measures are better when used serially to monitor a bleeding patient and future studies may provide more information about thresholds for transfusion and VHA use. ◆

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