Intraoperative management of coagulation

Introduction

Coagulopathy, blood loss and the use of allogenic blood products are independent risk factors for postoperative morbidity and mortality. Coagulation management begins preoperatively with assessment of the patient's risk, to identify those at high risk of bleeding but also those at risk of thrombosis.

The paradigm of patient blood management has been increasingly adopted to reduce unnecessary blood transfusions, and therefore improve patient outcomes after surgery. Patient blood management consists of three pillars:

1. The optimization of erythropoiesis,
2. Minimizing blood loss and bleeding
3. Harnessing patient reserve and tolerance of anaemia.

The first pillar should be addressed in the preoperative period. Intraoperative monitoring and management of the coagulation system is key to the second pillar.

The first of these articles (p. C71) discussed the coagulation system and tests of coagulation. This article will outline treatment strategies for managing coagulation.

Preoperative management

Coagulation management begins in the preoperative stage. Evidence-based guidelines such as the American College of Cardiology/American Heart Association guidelines exist to facilitate the risk assessment that must be made for the individual patient's thrombotic and bleeding balance (Fleisher et al, 2007).

Patients taking anticoagulant drugs such as warfarin are recommended to stop 5 days before surgery, and high-risk patients, such as those with mechanical heart valves, start on bridging anticoagulation (usually low molecular weight heparin). Reference to local protocols for bridging and liaison with a haematologist is recommended. Patients taking aspirin are advised to continue taking it in most situations, and if it is to be stopped, a time period of 5 days is recommended (Kozek-Langenecker et al, 2013).

Patients with coronary stents are recommended to continue taking antiplatelet agents if having surgery within 6 weeks of a bare metal stent placement, or 12 months of a drug-eluting stent placement. Awareness of the increased bleeding risk in those patients taking anticoagulants and antiplatelet agents is important.

Novel anticoagulant drugs

Novel anticoagulants include the direct factor Xa inhibitors (rivaroxaban and apixaban) and the direct thrombin inhibitor dabigatran. These have rapid onset and offset, and do not require routine laboratory monitoring unlike warfarin. For surgery with a low risk of bleeding, discontinuation for two half-lives (approximately 24 hours) before surgery is recommended before restarting 24 hours post surgery. For procedures at a higher risk of bleeding, 5 days is recommended, with bridging heparin as appropriate. Unlike warfarin, they are not reversible.

In the instance of bleeding or the patient requiring emergency surgery, the short half lives of these drugs means that discontinuation leads to a rapid decline in anticoagulant activity in patients with normal renal function. Elimination of dabigatran is renal dependant, and it has low protein binding, making haemodialysis a therapeutic option for dabigatran-related bleeding. For rivaroxaban and apixaban, when bleeding is life threatening, prothrombin complex concentrates can be considered (Levy et al, 2013). In all cases, a haematologist's opinion should be sought.

Intraoperative management

Monitoring

Conventional coagulation tests can fail to recognize the coagulation changes occurring intraoperatively, and are unable to detect fibrinolysis. The time to process samples and issue results (prothrombin time or international normalized ratio tests can require 90 minutes) make them inadequate to monitor changing conditions intraoperatively, particularly during major haemorrhage.

The type of surgery, e.g. vascular surgery or surgery requiring cardiopulmonary bypass, and the type and amount of fluid used influence coagulation. Coagulopathy secondary to blood loss is extremely variable between patients, as a result of differences in total circulating volume and initial haemostatic competence (Innerhofer and Kienast, 2010).

Point of care tests, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), can provide rapid, reliable results from whole blood samples upon which to base coagulation management. Transfusion requirements are reduced using point of care test-based protocols with pre-defined transfusion triggers rather than empirical or prophylactic treatment. European guidelines for the management of severe perioperative bleeding now exist (Kozek-Langenecker et al, 2013).

General measures

The triad of hypothermia, acidosis and coagulopathy must be avoided. Hypothermia decreases fibrinogen synthesis, the activity of proteases and the function of platelets (Bisbe and Moltó, 2013). Avoidance of acidosis and hypocalcaemia are important general steps in maintaining the efficiency of the coagulation system. Calcium concentration should be kept above 1.0 mmol/litre. Avoiding hypervolaemia from crystalloids and colloids is important in preventing the occurrence of a dilutional coagulopathy, dilutional anaemia and increased venous pressure, which can increase surgical bleeding.

The use of massive haemorrhage protocols to guide the use of red blood cells and other blood components, providing ratios of up to 1:1 of red blood cells and fresh frozen plasma, improves outcomes (Khan et al, 2013). Goal-directed transfusion algorithms using thromboelastography and rotational thromboelastometry should also be used to guide administration and monitor the response to treatment.

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Blood products and pharmacological treatments

Platelets

Platelet transfusion thresholds vary according to the type of surgery and platelet function. It is suggested that the platelet count should be maintained at between 50 and $100x10^9$/litre depending upon the type of surgery, e.g. in neurosurgery it is recommended to have a starting platelet count greater than $100x10^9$/litre. Platelets are often transferred from central transfusion laboratories and delays can occur when they are requested at short notice.

Fresh frozen plasma

Fresh frozen plasma is prepared from centrifuged whole blood or by apheresis. It is also available as a pathogen-reduced product to inactivate lipid-coated viruses. A typical unit of 300 ml includes 80 IU/ml von Willebrand factor, 100 IU/ml antithrombin III, 2.67 g/litre fibrinogen, 80 IU/ml factor II, 80 IU/ml factor V, 90 IU/ml factor VII, 92 IU/ml factor VIII, 100 IU/ml factor IX, 85 IU/ml factor X, 100 IU/ml factor XI, 83 IU/ml factor XII and 100 IU/ml factor XIII.

Fresh frozen plasma is indicated for patients who are bleeding with evidence of multiple coagulation factor deficiencies and to prevent dilutional coagulopathy in patients with major trauma and/or massive bleeding (Kor et al, 2010). It requires thawing, usually taking 20 minutes. The factor concentrations decrease progressively after thawing. Dosing recommendations begin at 10–15 ml/kg, but these volumes are generally inadequate to reliably restore coagulation factors (Chowdhury et al, 2004), increasing the risk of circulatory overload as greater volumes are given.

Prothrombin complex concentrates

Prothrombin complex concentrates are purified coagulation factors, concentrated from pooled plasma, with 25 times higher concentrations than plasma. They are virally reduced. They permit correction of coagulation using a small volume (approximately 40 ml), providing the vitamin K-dependent clotting factors II, VII, IX and X, and the coagulation inhibitors protein C and S.

Current evidence suggests that even in high risk patients, prothrombin complex concentrates are safe, but reported risks include thromboembolic events including venous thromboembolism, acute myocardial infarction and disseminated intravascular coagulation. Currently available prothrombin complex concentrates contain anticoagulants in contrast to earlier formulations, and thromboembolic events are rare. Prothrombin complex concentrates are recommended over fresh frozen plasma for rapid warfarin reversal since they provide more consistent and rapid normalization of international normalized ratio. Dosing is dependent upon the initial international normalized ratio and should be discussed with a haematologist.

Cryoprecipitate

Cryoprecipitate is a concentrated blood component made from fresh frozen plasma that is centrifuged, providing high concentrations of fibrinogen as well as factors VIII, XIII and von Willebrand factor. A typical adult dose of a volume of 200–500 ml will provide 3–6 g of fibrinogen and would typically increase fibrinogen levels by about 1 g/litre (McClelland, 2007).

Fibrinogen concentrates

It is now recognized that low fibrinogen levels are associated with massive bleeding, e.g. post-partum haemorrhage and trauma. In the case of active bleeding levels should be maintained at least at 1.5 g/litre. When haemodilution and massive bleeding occur, fibrinogen is the first factor to reach critical levels (Hiippala et al, 1995). Fibrinogen concentrates raise the fibrinogen level and improve clot strength. They have been used for many years in countries such as Austria and Germany where cryoprecipitate is not available for acquired bleeding disorders.

They are advised when plasma fibrinogen concentration is <1.5–2 g/litre or to increase the FIBTEM (fibrinogen thromboelastometry) or functional fibrinogen thromboelastography, at an initial dose of 25–50 mg/kg. In practice a 1 g dose should increase the fibrinogen concentration by 0.25 g/litre and a typical dose is 2–4 g. Increased fibrinogen concentrate can partially compensate for a low platelet count, restoring the maximum amplitude (MA) on thromboelastography.

Recombinant factor VIIa

Recombinant factor VIIa directly activates factor X, precipitating the conversion of prothrombin to thrombin, forming a haemostatic clot. Recombinant factor VIIa binds to the surface of activated platelet at sites of vascular injury, increasing local thrombin generation. However, it is associated with a significant increase in the incidence of arterial thrombotic events, so should never be given prophylactically, and only used as a rescue therapy for uncontrolled bleeding (Levi et al, 2010). A platelet count of greater than $30x10^9$/litre is required for it to be effective.

Tranexamic acid

Tranexamic acid is an antifibrinolytic drug. It is a lysine analogue, inhibiting fibrinolysis by binding to and inhibiting lysine binding sites on plasminogen, limiting the activation of plasmin that cleaves fibrin strands. The CRASH-2 trial demonstrated that early administration of a loading dose of 1 g followed by a 1 g infusion reduced all-cause mortality in trauma patients. Importantly, mortality rose if the initial dose was given after 3 hours (CRASH-2 collaborators et al, 2011). In elective surgery its use reduces the need for blood transfusion by a third in cardiac surgery and orthopaedics (Henry et al, 2011). It should be considered early in the management of intraoperative bleeding and in some cases repeated doses are required.

Protamine

Protamine is a polypeptide of arginine used to reverse unfractionated heparin. It is routinely administered after cardiopulmonary bypass to reverse heparin. However, it has a dose-dependent anticoagulant activity and excess protamine inhibits the coagulation cascade thereby contributing to the coagulopathy itself. It can cause adverse reactions including anaphylaxis, acute pulmonary vasoconstriction and hypotension. Sometimes a second dose of protamine is required 2–3 hours after the initial heparin reversal as a result of a heparin rebound. A heparinase thromboelastography or HEPTEM (heparinase modified thromboelastometry) can assess adequate reversal.

Special circumstances

Massive haemorrhage and trauma

Various definitions of massive haemorrhage are used. These include: >20% blood volume loss, the loss of one whole blood volume within 24 hours, or a rate of loss of

150 ml/minute (British Committee for Standards in Haematology et al, 2006). An acute trauma coagulopathy can ensue as a result of the combination of tissue injury and shock, deranging coagulation, and increasing mortality. Acute trauma coagulopathy is a global failure of the coagulation system driven by endothelial activation of endogenous anticoagulant protein C, followed by an anticoagulated state and a 'thrombin switch', such that less thrombin is available to cleave fibrinogen to fibrin. This is associated with rapid falls in fibrinogen levels in trauma patients, and hyperfibrinolysis (Davenport, 2013). The anticoagulated state is exacerbated by hypothermia, acidosis and iatrogenic haemodilution.

Restoration of the circulating volume must take into account the need to maintain tissue perfusion and oxygenation by red blood cells, but also the replacement of other blood components required for the maintenance of haemostasis, including platelets and plasma clotting factors.

Resuscitation with crystalloid and colloid solutions must be cautious to prevent an additional dilutional coagulopathy, while paying attention to the risk of hypothermia from cold fluids and acidosis secondary to tissue hypoperfusion. Massive haemorrhage protocols and goal-directed transfusion using point of care tests should be used to guide management. Tranexamic acid should be used to reduce bleeding.

Dilutional coagulopathy

Dilutional coagulopathy occurs as a result of consumption of fibrinogen, coagulation factors and platelets, blood loss, and as a result of excess fluid administration. This decreases the quantity of substrates available for thrombin generation, and alters the balance of activators and anticoagulants required for haemostasis. Colloids impair clot formation to a larger extent than crystalloids (Innerhofer and Kienast, 2010). Various mechanisms for this are proposed. Mild dilution reduces clot firmness, as a result of a disturbance in fibrinogen and fibrin polymerization. Thrombin generation is a product of platelets and fibrinogen and is maintained until profound dilution occurs. Fibrinogen deficiency occurs far in advance of other clotting factors, which can be diluted below 30% of normal levels before coagulopathy occurs. Thrombocytopaenia is a late phenomenon as a result of recruitment, e.g. from the spleen, and is generally not clinically relevant until platelet counts are below $50x10^9$/litre (Hiippala et al, 1995).

Disseminated intravascular coagulation

Disseminated intravascular coagulation is a syndrome associated with many critical illnesses including severe sepsis, malignancy, severe trauma, obstetric complications and liver disease. It occurs secondary to widespread over-activation of the coagulation system, leading to microvascular fibrin deposition, which contributes to multiple organ dysfunction, and consumption of coagulation factors and platelets. The resulting thrombocytopaenia and low levels of coagulation factors can lead to intractable bleeding.

Thrombocytopaenia is an important marker ($<100x10^9$/litre is seen in 50–60% of disseminated intravascular coagulation patients), and those with a platelet count of $<50x10^9$/litre have a 4–5x higher risk of bleeding (Levi and Meijers, 2011). As coagulation factors decline, a prolonged prothrombin time or activated partial thromboplastin time is seen once levels are below 50% of normal. Fibrinogen levels may remain normal since it is an acute phase reactant, although it is being consumed in disseminated intravascular coagulation. Fibrin degradation products are high in disseminated intravascular coagulation, but this can be indistinguishable from patients who have recently undergone surgery or have venous thromboembolism. Low levels of coagulation inhibitors such as protein C and antithrombin III are common in disseminated intravascular coagulation.

The International Society of Thrombosis and Haemostasis has designed a scoring system for diagnosing disseminated intravascular coagulation based upon routine tests: platelet count, prothrombin time or international normalized ratio, fibrin-related markers (usually d-dimers) and fibrinogen (Levi and Meijers, 2011). If diagnosed, sequential monitoring of coagulation is recommended. The management of disseminated intravascular coagulation is aimed at treating the underlying disorder, while providing supportive treatment to the coagulation abnormalities as clinically required. In general a platelet count of $>50x10^9$/litre should be maintained, and specific coagulation factors including fibrinogen can be applied when deficiencies are identified. Replacement of platelets and clotting factors should not be performed on the basis of abnormal laboratory results without evidence of active bleeding.

Liver disease

Liver disease is associated with a coagulopathy, demonstrated by a raised international normalized ratio, which led to an assumption that such patients were auto-anticoagulated and also had an increased risk of bleeding. In chronic liver disease, all pro-coagulant factors are decreased (except factor VIII and von Willebrand factor, which increase). Balancing this is a decrease in anticoagulant factors, protein C and S, antithrombin.

The rise in von Willebrand factor, which promotes platelet aggregation, is balanced by thrombocytopaenia and platelet function defects. Overall, haemostasis is re-balanced, but with a lower haemostatic reserve, so that the risk of being tipped towards bleeding or thrombosis is increased compared to in health. However, conven-

TOP TIPS

- Coagulation management begins with maintaining optimum conditions for haemostasis: avoiding hypothermia (keeping temperature >34°C), acidosis, and hypocalcaemia (maintain calcium >1 mmol/litre).
- Refer to local protocols of the management of major bleeding and liaise early with a haematologist.
- Fluid replacement should be cautious to avoid a dilutional coagulopathy, and be aware that colloids have a direct impact upon clot formation.
- Consider the early use of antifibrinolytic drugs if there is bleeding.
- The use of fibrinogen concentrates (or cryoprecipitate) should be considered, and a fibrinogen concentration >2 g/litre maintained.

tional tests of coagulation, including prothrombin time or international normalized ratio, fail to measure this, since only the procoagulant factors are measured. Thus, a raised international normalized ratio has been shown to misrepresent the increased risk of bleeding (Tripodi and Mannucci, 2011).

Obstetrics

Obstetric haemorrhage remains a common cause of maternal mortality in the UK, and the leading cause of maternal death worldwide. Haemostasis is altered during pregnancy, leading to a procoagulant state, which may reduce the risk of haemorrhage. However, the physiological anaemia of pregnancy and thrombocytopaenia increase the risk of bleeding and blood transfusion requirements. The thrombocytopaenia is multifactorial: gestational (75%), caused by pre-eclampsia, the HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), acute fatty liver and disseminated intravascular coagulation are all causative.

Normal losses are 500 ml blood loss after vaginal delivery and 1000 ml after caesarean section, and volumes above this represent peripartum haemorrhage. In the event of post-partum haemorrhage, focus must include uterine atony as the major cause (75%), the response to placental tissue, peripartum tissue damage, and enhanced thrombin generation, hyperfibrinolysis and defibrination. Major obstetric haemorrhage protocols should be used with efforts to increase uterine tone using uterotonics and surgical compression, while maintaining normothermia, neutral pH and replacing calcium.

Fibrinogen levels correlate with the severity of post-partum haemorrhage (Charbit et al, 2007). A level of <2 g/litre in early post-partum haemorrhage is associated with the development of severe bleeding and should be treated with prothrombin complex concentrates or fresh frozen plasma and the use of antifibrinolytics such as tranexamic acid.

Conclusions

The management of coagulation and bleeding risk for surgery begins in the preoperative period with a thorough past medical history and an individual perioperative plan made, depending upon surgical and patient factors. The use of protocols for transfusion of blood, blood products and clotting factors has been shown to reduce transfusion requirements and improve outcomes after surgery. Intraoperative bleeding is caused by multiple factors, but can now be more readily monitored using point of care testing. A multimodal approach should be implemented when dealing with coagulopathy and haemorrhage. **BJHM**

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KEY POINTS

- Preoperative assessment of a patient for bleeding risk is paramount to be prepared for coagulopathy and haemorrhage.
- Consider the effect of anticoagulant drugs and antiplatelet drugs upon patients perioperatively and liaise with a haematologist when patients are taking these drugs or present a bleeding history preoperatively.
- The use of point of care test-guided protocols intraoperatively reduces haemorrhage and transfusion requirements.
- A multimodal approach to coagulation management should be used including surgical control of bleeding, temperature maintenance, correction of acidosis and hypocalcaemia, the use of anti-fibrinolytics, factor concentrates and blood products
- Prothrombin complex concentrates provide coagulation factors in predictable doses and low volumes, and should be the first line for the rapid reversal of warfarin.
- Major haemorrhage protocols for trauma and obstetrics should be implemented to guide bleeding management.
- Platelets and fresh frozen plasma transfusions, as well as red blood cell transfusions, have risks and hazards that should be considered.