https://doi.org/10.60115/11055/1187

The tightrope of haemostatic homeostasis – perioperative methods for coagulation factor manipulation

Tom Fox MBBS MRCEM FANZCA

Department of Anaesthesia, Royal Adelaide Hospital, Adelaide, Australia

Dr Tom Fox has recently completed fellowships in neuroanaesthesia and airway and has a developing interest in patient blood management. He is a newly appointed staff specialist at the Royal Adelaide Hospital.

Kate Drummond MBBS FANZCA GCertClinUS MPeriopMed

Department of Anaesthesia, Royal Adelaide Hospital, Adelaide, Australia; Specialist Anaesthetist, Pulse Anaesthetics, Adelaide, Australia; Clinical Senior Lecturer, University of Adelaide Medical School, Faculty of Health and Medical Sciences, Adelaide, Australia

Dr Kate Drummond is a staff specialist anaesthetist at the Royal Adelaide Hospital and works in private practice with Pulse Anaesthesia. She has a master's degree in perioperative medicine and her special areas of interest include perioperative medicine, with a focus on blood management, and cardiothoracic anaesthesia and transoesophageal echocardiography.

Edited by Dr Gerald Toh

A BRIEF HISTORY OF CLOTTING FACTOR DEVELOPMENT

To fully comprehend the advanced and complex options currently available to treat inherited disorders of coagulation, we must first return to a time, just 100 years ago when the prognosis of haemophilia was dire. The only treatment for severe debilitating bleeding and haemarthrosis was splinting, ice, and bedrest. Life expectancy was only 10-15 years, even for patients with mild disease. Those lucky few that did survive were compromised by severe disability.[1]

During the First World War, high numbers of casualties forced medical advancement and the understanding of blood types. This resulted in a low efficacious treatment option for haemophilia; patients were given whole blood, which contained the missing coagulation factors they needed. With only a modest clinical benefit, life expectancy improved to around 20 years of age.[2]

Over time, increasing combat casualties became triggers for the improved preparation of plasma, that contained coagulation factors alone. However, this form of replacement therapy was not widely available and was also of limited clinical efficacy. So, even until the 1960s, the life expectancy of patients with haemophilia was no more than 20-30 years.[2]

In 1964 Judith Pool discovered cryoprecipitation, the process for creating concentrated blood clotting factors including human Factor VIII.[3]

By the 1970s, industrial scale processes were in place for manufacturing factor concentrates, which significantly improved the quality of life for patients with haemophilia, who had access to such treatment. From then on Factor VIII was available to terminate acute bleeding caused by haemophilia, and to preoperatively prepare the patient for surgical procedures previously deemed too high risk.[3]

However, the 1980s saw a dramatic and devastating blight on this progress. Patients treated with clotting factors produced from large plasma pools began contracting blood-borne infections, most notably HIV and hepatitis.[4] Then in the 1990s, advancements in molecular genetics allowed the manufacture of recombinant factors and this, in combination with enhanced screening and virucidal techniques, has halted the transmission of blood-borne viruses, with no reported cases since 1990.[4]

Unfortunately, blood-borne diseases was not the only significant obstacle encountered by patients with inherited clotting disorders, as it emerged that up to one third of patients treated with factor-specific therapies would go on to develop alloantibodies to the factor they received.[5] This made them refractory to replacement therapy because the coagulant activity contained in factor replacement products was neutralised by the patient's own specific antibodies.

Alternative ways of achieving clotting were sought and it was discovered that plasma concentrates of activated factors of the prothrombin complex (aPCC), as well as the recombinant production of activated Factor VII (rFVIIa), offered new ways to bypass the coagulation defect associated with Factor VIII inhibitors. These were termed "bypass agents" and have been extremely successful in improving outcomes for patients with inherited

bleeding disorders, such that their life expectancies now approach those of a person with no clotting disorder.[4] Further advances include the discovery of extended half-life factors, which increase the dosing interval for patients with severe disease who require regular factor therapy. In today's practice, we have access to several purified factor concentrates for use in trauma, cardiac, and obstetric surgery and this is largely thanks to our understanding of the inherited clotting disorders such as the different types of haemophilia, which have been the driving force for progress regarding factor fractionation.

INTRODUCTION

This paper will review the currently available factor concentrates and the evidence and indications for use. Figure 1. summarises the currently available factor preparations available in Australia that will be covered in this article.

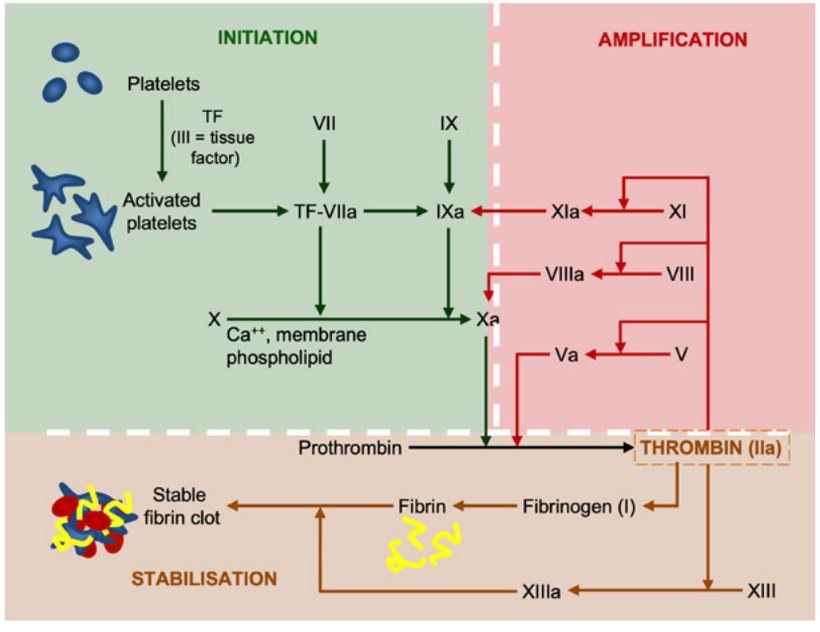
Figure 1. Products available in Australia[6]

	Trade name	Source	Indications	Off label use	Dose*	Cost
I	RiaSTAP	Human plasma	Acute bleeding and prophylaxis in patients with congenital fibrinogen deficiency	Dysfibrinogenemia (acquired deficit)	Trauma/ acquired deficiency 50-70 mg/kg Congenital fibrinogen deficiency – dose calculated according to target levels and current levels	$863/g
VIIa	NovoSeven	Recombinant	Haemophilia A or B with inhibitors Acquired haemophilia Glanzmann thrombasthenia, congenital Factor VII deficiency	Salvage therapy to control microvascular bleeding	Haemophilia 90 mcg/kg Cardiac surgery 30 mcg/kg[7]	$1350/ mg
VIII	Eloctate Adynovate	Human plasma Recombinant	Haemophilia A		Prophylaxis 40-50 IU/kg Max 70 IU/kg	
IX	Alprolix	Human plasma Recombinant	Haemophilia B		Prophylaxis 50 IU/kg Major bleed 133 IU/kg	
XI	Hemoleven	Human plasma	Severe Factor XI deficiency with no inhibitor		15 units/kg	$14/IU
XIII	Fibrogammin	Human plasma	Factor XIII deficiency		25-40 IU/kg	$214/ 250IU
vWF + VIII	Biostate	Human plasma	Willebrand disease,	Haemophilia A	Seek haematology advice	$960/ 1000 IU
Anti-thrombin III	Thrombotrol	Human plasma	Hereditary or acquired AT deficiency	Heparin resistance	Dose required = (desired level – pretreatment level) x weight in kg x 2.2	$1547/ 1000IU
II, IX, X,	Prothrombinex	Human plasma	Rapid normalisation of vitamin K dependent clotting factors		25-50 IU/kg depending on extent of INR derangement.	$305/ 500IU
*Seek haematology advice before prescribing any specialist clotting factors						

FACTOR 1 (FIBRINOGEN)

Fibrinogen (Factor I) is a glycoprotein complex produced by the liver and plays a pivotal role in the stabilisation phase of clot formation in haemostasis (Figure 2). During tissue and vascular injury, it is converted enzymatically by thrombin to fibrin and then to an insoluble fibrin-based clot. It supports thrombin generation and platelet aggregation and facilitates wound healing.[8]

Figure 2. Clotting factors involved in the initiation, amplification, and stabilisation of clot formation



Factor 1 (fibrinogen) is available from fresh frozen plasma (FFP), cryoprecipitate, or as a fibrinogen concentrate (RiaSTAP®). The quantity of Factor I varies significantly depending on the product. Hence the volume of infusion required for a clinically effective dose varies depending on the product used. Fibrinogen concentrate contains 20g/L of Factor I, compared to 15-17g/L for cryoprecipitate and 2g/L for FFP.[9] Additionally, there are several benefits of fibrinogen concentrate including being blood type free, storage at room temperature, and rapid reconstitution and administration. Cost is the main barrier to its widespread use. Cryoprecipitate, on the other hand, has the advantage of containing other important coagulation factors such as von Willebrand Factor (vWF), Factor VIII, and Factor XIII, which may promote more rapid and effective coagulation in bleeding patients.[9]

Congenital fibrinogen deficiency is a rare, autosomal recessive inherited bleeding disorder in which coagulation is impaired by lack of fibrinogen. The lack of fibrinogen expresses itself with excessive and, at times, uncontrollable bleeding most commonly occurring at birth from the umbilical cord.[10]

INDICATIONS FOR USE

In Australia and New Zealand, fibrinogen concentrate is supplied and funded for treatment of acute bleeding and prophylaxis in patients with congenital fibrinogen deficiency (including afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia).[11,12]

The most common off label use for fibrinogen concentrate is in the management of major bleeding as an alternative to cryoprecipitate. Fibrinogen concentrate leads to faster correction of fibrinogen levels compared with cryoprecipitate.[13] However, cryoprecipitate transfusion provides additional factors that restore key fibrinolytic regulators and limit plasmin generation. Consequently, cryoprecipitate led to stronger and more stable clots with a more natural fibrin structure compared with fibrinogen concentrate in an ex vivo study.[14] A large randomised controlled trial comparing fibrinogen concentrate and cryoprecipitate use early in trauma on clinical, patient-centred outcomes is ongoing (FEISTY II).[15]

FACTOR VIIA (NOVOSEVEN™)

Factor VIIa, when bound to tissue factor (Factor III), is important in the initiation phase of clot formation. Factor VII circulates in the blood in the inactive form. Upon vessel injury, Factor VII is exposed to tissue factor (TF) and activated to become Factor VIIa by proteases, among which are thrombin (Factor IIa), Factors Xa, IXa, XIIa, and the Factor VIIa-TF complex itself. The complex of Factor VIIa-TF catalyses the conversion of Factor IX to IXa and Factor X to Xa (Figure 2).[16]

NovoSeven™ is a recombinant Factor VII in an activated form. As Factor VIIa has already been activated, thereby bypassing the body's innate homeostasis, it carries greater risks of thrombosis than other factor products. Clinicians must incorporate clinical judgment to balance the potential benefits of achieving haemostasis against the higher risks of thrombosis when administrating this product.

NovoSeven™ was developed for patients with inhibitors to coagulation Factor VIII or Factor IX, and congenital Factor VII deficiency. It is generated in cultured hamster cells grown in newborn calf serum (purified from culture supernatant) and is converted to Factor VIIa during purification.

INDICATIONS FOR USE

In Australia and New Zealand, NovoSeven™ has been approved for several indications (no age limit) including Haemophilia A and B with inhibitors, acquired haemophilia, Glanzmann thrombasthenia, and congenital Factor VII deficiency.[17] It has an ultra-short half-life of just 2.6 to 6 hours after administration. The initial dose is 90 mcg/kg however there is significant individual variability in the haemostatic response to Factor VIIa, and it can be prothrombotic in non-haemophiliacs.[17]

The off-label use of NovoSeven™ is generally reserved as salvage therapy to control microvascular bleeding when conventional therapy with transfusions and antifibrinolytic therapies have failed. Use under these circumstances has been investigated by multiple RCTs and subsequently a meta-analysis of 993 uses which concluded that rFVIIa did not change mortality (RR, 0.90; 95% CI: 0.50, 1.64; I 2 = 0.0%; P = 0.738).[18]

Individual RCT analyses showed that the use of rFVIIa could reduce the volume of blood loss (including for prostate cancer, severe acute pancreatitis (SAP), and spinal disease) and the transfusion of packed red cells (PRC) and FFP in subsets of perioperative patients. There was also a trend toward reduced surgical re-exploration in cardiac surgery, but this did not meet statistical significance.[18]

Recommendations endorsed by the European Society of Anaesthesiology cited the lack of good evidence for the use of rFVIIa which limits the scope of its use. In summary, there is a rationale for using rFVIIa to treat massive bleeding in certain indications, but only adjunctively to the surgical control of bleeding once conventional therapies have failed.[19] Additionally, it is worth noting the current cost of rFVIIa in Australia is around $6000 for a single adult dose.[6]

FACTOR VIII

Factor VIII is essential for forming a stable blood clot (Figure 2). Factor VIII circulates in a stable noncovalent complex bound with vWF. When tissue is damaged, it is activated by thrombin (Factor IIa) and dissociates from vWF. It then binds to and becomes a cofactor for Factor IXa to activate Factor X, which, in turn, with its cofactor

Factor Va, activates more thrombin. This sets up a positive feedback loop contributing to a 'thrombin burst'. Thrombin cleaves fibrinogen into fibrin which polymerises and crosslinks – using Factor XIII – into an insoluble blood clot.

Factor VIII deficiency results in Haemophilia A. Most commonly, Haemophilia A is a hereditary disorder with an X-linked recessive inheritance pattern and therefore more likely to affect males. It has an incidence of 1 in 5000 male births. Disease can be mild, moderate, or severe depending on the level of activity of Factor VIII. Around 30% of female carriers have Factor VIII activity below 40% and are at risk of increased bleeding in the perioperative period.[20]

Acquired Haemophilia A, an autoimmune disorder, is much rarer (1-6 cases per million inhabitants per year) and is caused by the development of autoantibodies against Factor VIII.[21] About half of acquired Haemophilia A cases are idiopathic. There is, however, an association with the postpartum period, drugs (penicillin, sulfonamides, phenytoin, interferons, fludarabine), other systemic autoimmune diseases – such as rheumatoid arthritis, malignancies, and infections.[21]

Factor VIII therapy is available in three forms, plasma-derived, recombinant, and extended half-life recombinant. Plasma-derived Factor VIII concentrates are prepared by commercial fractionation of carefully screened donor plasma. They are stratified based on purity. Greater purity reflects a higher ratio of Factor VIII to non-Factor VIII proteins. Recombinant Factor VIII products include several genetically engineered proteins produced in either animal or human cell lines. For the most part, these are made using modified versions of the human Factor VIII gene.[22] Longer-lasting recombinant Factor VIII preparations with extended half-lives have the advantage of less-frequent dosing, enhancing the ease of administration for some patients. This is now the gold standard for haemophilia care with Eloctate and Adynovate being the main commercially available products.[23]

The dose for prophylaxis for severe Haemophilia A is 25-40 units/kg, 3 times per week. Levels are monitored via Factor VIII assay with the units reported as a percentage of normal. The dose in emergency bleeding will vary depending on factor levels and is best guided by a haemophilia treatment centre (HTC).[24]

Currently there is no indication for the use of Factor VIII in the perioperative period other than in the management of haemophilia.

FACTOR IX

Factor IX is cleaved by Factor XIa of the contact pathway or Factor VIIa of the tissue factor pathway to form Factor IXa. Then Factor IXa, in the presence of Ca2+, membrane phospholipids, and a Factor VIII cofactor, hydrolyses one arginine-isoleucine bond in Factor X to form Factor Xa which helps begin the initiation of clot formation. Factor Xa is required to convert prothrombin to thrombin. However, if antithrombin is present, Factor IX is inhibited.[25]

Deficiencies in Factor IX manifest as Haemophilia B, also known as Christmas disease, presents with a range of severities depending on the gene defect. Although it is the second most common haemophilia, it is generally less severe than Haemophilia A.[26] It too, is inherited as an X-linked recessive disorder. Female carriers are usually asymptomatic.

Again, like Factor VIII there are three formulations. Plasma-derived Factor IX, recombinant Factor IX, and extended half-life recombinant Factor IX (Alprolix being the most widely used).[4]

In the absence of an inhibitor, the dose required is obtained by multiplying the patient's weight in kilograms by the desired factor level. Each international unit (amount in 1 mL of normal pooled plasma) of Factor IX per kilogram of body weight will raise the plasma Factor IX level by about 1 IU/dl.[27] For example, a 50 kg patient who needs a level of 40 IU/dl would need 2000 units of plasma-derived Factor IX. Vials of Factor IX concentrates are available in doses ranging from 250 to 3000 units each.

FACTOR XI

Factor XI deficiency, Haemophilia C, is an extremely rare condition with prevalence around 1 in 1 million that is usually inherited in an autosomal recessive pattern.[28,29] This condition shows a significant clinical heterogeneity depending on the degree of factor deficiency. It is thought that Factor XI is more important in developing thrombosis, rather than haemostasis, although some case series report higher rates of epistaxis, menorrhagia, and perioperative or post-partum bleeding.[29] The condition is usually much less severe than other forms of haemophilia, usually with minimal impact on patients' daily lives.

Given the rarity of this condition, Haemoleven (Factor XI) is not routinely kept in HTCs and may have to be ordered well in advance if required. It is indicated for prophylaxis in major surgery or for treatment of bleeding in severe Factor XI deficiency with no inhibitor.

If the inhibitor screen is positive, then it is advised to use Factor VIIa as a bypass agent instead. However, most surgical procedures do not require prophylaxis as the coagulation defect tends to be mild. For minor procedures or mild disease, individuals may reasonably choose expectant management or antifibrinolytic therapy. Hemoleven is a high-purity Factor XI concentrate derived from human plasma. The dose should be no more than 10-15 units/kg and there is a 10% thrombosis risk. A reasonable alternative is FFP for emergency situations or when Factor XI is unavailable.[30]

FACTOR XIII

Factor XIII deficiency is an autosomal recessive inherited bleeding disorder, characterised by spontaneous and provoked bleeding from sites such as the umbilical cord, or surgical, joint, and intracranial haemorrhages in patients who are homozygous. Menorrhagia, recurrent miscarriage, and impaired wound healing are also widely reported.[31-33] Heterozygous carriers may show a bleeding tendency upon provocation such as traumatic injury or invasive procedures and in some cases, umbilical cord bleeding, menorrhagia, miscarriages, or postpartum bleeding.[34]

Factor XIII levels of less than 15% of normal have been established as the threshold at which bleeding risk is significantly elevated.[35] However in some patients, effective haemostasis can be achieved with Factor XIII levels as low as 2-5% depending on genes involved in the mutation.[36]

There are several Factor XIII replacement products commercially available including recombinant Factor XIII A-subunit (Tretten) and Factor XIII purified from human plasma (Fibrogammin and Fibrogammin-P).[37] Unlike most other coagulation factors, Factor XIII has a significantly longer half-life of 9-14 days and as such, replacement may be undertaken as infrequently as once per month.

The recommended dose is 25-40 IU/kg administered intravenously. For hospitals that do not have access to purified Factor XIII concentrate, FFP or cryoprecipitate can also be used to supply Factor XIII in an emergency. Factor XIII content in cryoprecipitate is 60IU and in FFP is 288IU.[38]

Perioperative dosing is the same dosing for treatment of spontaneous bleeding (25-40 IU/kg). It is important to note that if a routine prophylaxis dose has been given in the previous seven days, further doses are unlikely to be required. Recent Factor XIII levels and inhibitor screening are suggested preoperatively. Factor XIII replacement products are generally well tolerated. The major disadvantages are limited availability due to low stock kept in most centres and high cost.

VON WILLEBRAND FACTOR AND BIOSTATE

Biostate is a plasma-derived factor product containing both Factor VIII and vWF in a ratio of 1:2 (250 IU FVIII and 500 IU VWF). It is used as prophylaxis and treatment of non-surgical and surgical bleeding and in patients with von Willebrand Disease when desmopressin (DDAVP) treatment is ineffective or contraindicated. It is also effective in Factor VIII deficiency due to Haemophilia A. Dosing is complicated and it is highly recommended that clinicians seek advice from an HTC for guidance.

PROTHROMBIN COMPLEX CONCENTRATE

Prothrombinex, Beriplex, and Octaplex are all commercially available prothrombin complex concentrates (PCC). They all contain human plasma-derived vitamin K-dependent clotting Factors II, IX, X, variable amounts of Factor VII, and proteins C and S. Prothrombinex contains no Factor VII, while Beriplex P/N 250 contains 100-250 IU per vial and Beriplex P/N 500 contains 200-500 IU per vial.[39] Potency of PCC preparations is standardised to Factor IX content (e.g. 500 IU/vial).

The contents and indications of available PCCs are summarised in Figure 3.

Figure 3. Contents, approved indications, and off label uses for PPCs[40]

Concentrate	Coagulation factors functional component(s)	Indications	Off-label use/remark
4F-PCC	Coagulation factors II, VII, IX, X	Treatment and perioperative prophylaxis of bleeding in Acquired deficiency of PCC factors, such as deficiency caused by treatment with vitamin K antagonists Congenital deficiency of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available	Treatment of trauma-induced coagulopathy Treatment of bleeds in patients with liver disease Reversal of anticoagulation by direct Factor Xa and thrombin-inhibiting oral anticoagulants (evidence based on several bleeding models in animals and human volunteers; substantial clinical evidence is lacking)
3F-PCC	Coagulation factors II, IX, X	Prevention and control of bleeding in Haemophilia B patients	Anticoagulant reversal agent for for vitamin K antagonists (4F-PCC is superior to 3F-PCC) for direct oral thrombin and factor Xa inhibitors (evidence based on a few bleeding models in animals; substantial clinical evidence is lacking)
Activated-PCC	Coagulation factors II, IX, X, VII-activated form	Treatment and prophylaxis of bleeding in patients (Haemophilia A and B as well as non-haemophiliacs) with inhibitors to Factors VIII or IX	Anticoagulant reversal agent for vitamin K antagonists (evidence based on a limited number of clinical studies) direct oral thrombin and factor Xa inhibitors (evidence based on bleeding models in animals; substantial clinical evidence is lacking)

The main benefits of PCCs are that they are low volume, permit rapid administration, and are readily available and cheap. It is indicated for the rapid normalisation of vitamin K-dependent clotting factors within 30 minutes. The dose is 25-50 IU\kg depending on extent of INR derangement. Generally, 1 IU\kg of Factor IX raises the Factor IX by approximately 1%.

The most common use of PCC in Australia is for the reversal of warfarin, although there is increasing use in off-label use for the management of trauma induced coagulation defects. When used in Haemophilia B, repeated doses result in the accumulation of Factor X due to its much longer half-life compared with that of Factor IX. Venous thromboembolism and disseminated intravascular coagulation have been reported after multiple doses.[41]

ANTITHROMBIN CONCENTRATE (THROMBATE III OR THROMBOTROL®-VF)

Antithrombin functions primarily by deactivating thrombin and activating Factor X and secondarily by deactivating Factors VII, IX and XII. Levels less than 60% result in thrombosis. Thrombate III is a plasma-derived concentrate made from pooled human plasma indicated for hereditary or acquired AT deficiency in the prevention of venous thromboembolism.[42] Antithrombin concentrates are also used in cardiac surgery for the management of heparin resistance as an alternative to FFP.[43]

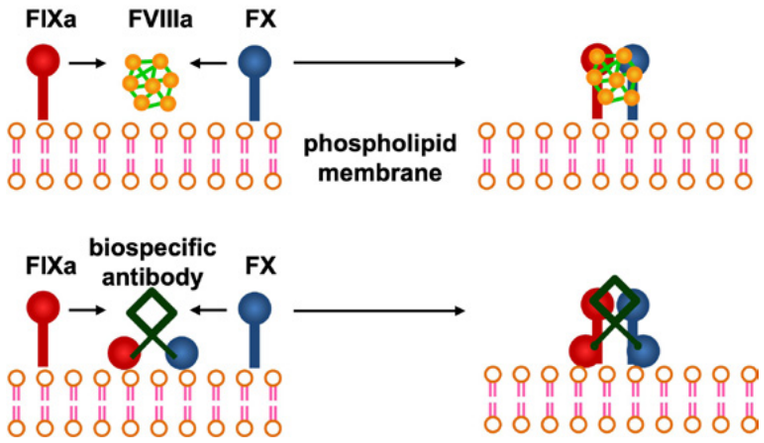
NON-FACTOR THERAPY – EMICIZUMAB

Emicizumab (Hemlibra) is a recombinant humanised monoclonal antibody that binds to Factors IXa and X simultaneously, bringing these two molecules together and substituting for Factor VIIIa as a cofactor for Factor IXa in activating Factor X (Figure 4).[44] This novel monoclonal antibody is an option for prophylaxis in individuals with Haemophilia A with or without inhibitors. However, it is not effective for the management of acute bleeding as it takes up to four weeks to achieve therapeutic effect.

Therapy is started with a loading dose of 3 mg/kg subcutaneously once weekly for four weeks. Subsequent maintenance dosing regimens are 1.5 mg/kg subcutaneously once per week, 3 mg/kg subcutaneously once every two weeks, or 6 mg/kg subcutaneously once every four weeks.

An adequate coagulation response is usually achieved within 4 weeks however there is no routine monitoring of coagulation status with emicizumab as standard aPTT-based coagulation tests and Factor VIII activity assays are affected by emicizumab itself and are therefore inaccurate. If an individual receiving emicizumab prophylaxis requires Factor VIII infusions, the Factor VIII activity and inhibitor titres must be measured using a bovine substrate-based chromogenic assay instead of the standard assay.[45] Haematology input is recommended in this situation.

Figure 4. Mechanism of action of emicizumab in the activation of Factor Xa[44]



ELECTIVE SURGERY

Planning for elective surgery should include the patient, family or caregivers, and all relevant clinicians to ensure that best practices are followed. Patients will often have a good understanding of their condition and know which clinical team to contact for advice. This multidisciplinary approach is outlined in detail in the *Guidelines for Management of Haemophilia in Australia* which is a very useful resource for perioperative clinicians.[46]

These guidelines emphasise the importance of collaborating with experts from an HTC to develop a haemostasis plan to cover the entire perioperative period. Preoperative assessment should include factor assays and inhibitor assays in addition to usual blood tests. It is important to focus on targeted factor replacement in preference to cryoprecipitate or FFP.

Surgery should ideally be undertaken at a centre with access to laboratory monitoring of factor activity levels and immediate availability of replacement factor concentrates. It is useful to care for these patients in hospitals affiliated with an HTC to allow timely and regular communication with the surgical teams and the patient's treating haematologist.

Patients should have their haemoglobin and coagulation optimised preoperatively and meticulous surgical technique should be used, with local haemostatic agents as appropriate. Where possible, procedures should be scheduled for early in the week and early in the day to allow for any management of complications in the following weekday and daylight hours.

In addition, postoperative screening for inhibitors in those that have received factor concentrate for the first time is recommended to detect those patients that have developed inhibitors as this will significantly affect future management.

EMERGENCY SURGERY

Emergency surgery presents additional challenges in what is usually an already challenging situation for patients with an inherited bleeding disorder. Under the guidance of the local HTC, urgent infusion of factor to raise the factor activity to a level appropriate for the procedure is likely to be recommended. Emergency surgical procedures may need to be conducted in non-HTCs. In these cases, surgery should be performed in close consultation with the staff of HTC.[46]

HOSPITALS WITH LIMITED BLOOD PRODUCT RESOURCES

Rural and remote settings may not have access to purified factor concentrates. Options here include the traditional approach of using FFP and cryoprecipitate (or indeed whole blood if available). For patients with Haemophilia A consider cryoprecipitate as an alternative option if available, as each bag will contain approximately 140IU of Factor VIII.[47]

CONCLUSION

In the past decade, there has been tremendous progress in coagulation factor fractionation adding to the available treatment options at our disposal. This is not only of benefit to patients with inherited clotting disorders but also those involved in major trauma, cardiac surgery, and obstetrics. The different types of haemophilia have been the driving force for progress in this area and as such, we have witnessed dramatic improvement in the prognosis for this group of patients.

Coagulation is a complex process and perioperative management of patients with inherited clotting disorders requires specialist haematologist involvement via the local HTC. Anaesthetists need to have a good understanding of coagulation in vivo to understand why patients might be bleeding, and in vitro to accurately interpret the cause of abnormal coagulation test results. An understanding of the perioperative role of the major factor concentrates allows anaesthetists and perioperative physicians to undertake and oversee multidisciplinary decisions and care to assure optimal outcomes for patients.

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