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Peri-operative management of patients with coagulation disorders

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Coagulation problems may be broadly divided into disorders of haemostasis and disorders of thrombosis, although there is a small intermediate group which involves both disorders. The special requirements of such patients in the peri-operative period will be discussed in the setting of the underlying condition.

Inherited disorders of haemostasis

A broad classification of the inherited disorders of haemoplasm is set out in Table 1.

The haemophilias

The haemophilias are characterized by a deficiency of coagulant factor which leads to increased bleeding at surgery and in the postoperative period. In the absence of platelet dysfunction, the bleeding time is normal.

Haemophilia A and haemophilia B

Haemophilia A, the most common of the haemophilias, is associated with deficiency of factor VIII coagulant protein. Haemophilia B (Christmas disease) is caused by deficiency of factor IX coagulant protein. Both these conditions have sex-linked recessive inheritance, affected males being born to carrier females, although up to 50% of cases appear *de novo* as a result of new mutations. The clinical severity of bleeding relates directly to the degree of deficiency. Spontaneous bleeding, classically haemarthroses, occur in severe cases (<2% coagulant factor VIII) while the moderately deficient (2–10% coagulant factor VIII) and those mildly affected (>10% coagulant factor VIII) may be expected to bleed excessively only after trauma or surgery. Some of the carrier females have significantly reduced coagulation factors and may behave clinically as mild cases themselves. This is particularly important in obstetric practice and in the peri-operative period, when specific replacement therapy may be required.

Over the last 50 yr, there has been progressive refinement in the provision of specific coagulant factor replacement therapy from fresh whole blood to the plasma-free recombinant products which have become available in the last 10 yr. In the intervening period, coagulation factor concentrates were obtained by fractionation from human plasma pooled from several thousand donations. Before the introduction of viral inactivation in 1985, the vast majority of patients treated with concentrate, which was thus derived from pooled plasma, contracted transfusion-transmitted hepatitis C (HCV) and half of those in the UK with severe haemophilia also acquired the human immunodeficiency virus (HIV).

In view of this history, therapeutic strategies to replace coagulation factors are also designed to minimize exposure to plasma components wherever possible.[47] Recommended therapeutic products are described in Table 2. For major surgery, a target concentration of 100% factor VIII is set to be maintained for the first 5–7 postoperative days, whereas minor procedures may be adequately covered by concentrations of 50% after the first day. Doses of factor VIII required to meet these targets are listed in Table 3. Many patients with moderate or mild haemophilia A produce a 2- to 4-fold increase in factor VIII in response to 1-deamino-8-D-arginine vasopressin (DDAVP), which will be adequate to cover minor surgery. Where higher concentrations are required, recombinant coagulant factor concentrate is the recommended replacement for all new patients and for children under 16 yr with haemophilia A and haemophilia B. For those over 16 yr, already established on treatment, high-purity coagulant factor replacement may be used. Since 1985, all such plasma products have been subjected to viral inactivation by heat treatment or a solvent detergent method

Table 1 Inherited disorders of haemostasis

Disorder	Pathophysiology (deficiency or defect)	Inheritance	Incidence per million
Haemophilia A	Factor VIII	X-linked recessive	100
Haemophilia B (Christmas disease)	Factor 1X	X linked recessive	20
Haemophilia C	Factor X1	Autosomal dominant or recessive	5% Ashkenazi Jews (others rare)
Von Willebrand's disease	Von Willebrand factor	Autosomal dominant or recessive	>100
Factor X deficiency	Factor X	Autosomal recessive	1
Factor V deficiency	Factor V	Autosomal recessive	1
Factor VII deficiency	Factor VII	Autosomal rececessive	1
Prothrombin deficiency	Factor II	Autosomal rececessive	1
Afibrinogenaemia	Factor I		1
Factor XIII deficiency	Factor XIII		1
Factor V plus VIII deficiency			1
Dysfibrinogenaemia	Factor I	Autosomal dominant	1

Table 2 Therapeutic materials for the treatment of haemophilia

Material	Factor VIII	Von Willebrand factor	Advantages	Disadvantages
DDAVP	–	–	No risk infection	Only effective in mild cases Tachyphylaxis
Intermediate-purity factor VIII concentrate	20–50 IU ml^{-1}	20–50 IU ml^{-1}		Non-factor VIII proteins present Plasma-derived
High-purity factor VIII concentrate	= 5000 IU mg^{-1} before addition of albumin carrier	–	Convenience	Plasma-derived Expensive
Recombinant factor VIII	= 5000 IU mg^{-1} before addition of albumin carrier	–	PureNo risk of infection	Very expensive Limited supply

to kill viruses with a lipid envelope (e.g. hepatitis B virus, HCV and HIV). More recently, an additional terminal filtration step has been introduced by some manufacturers to prevent the transmission of viruses which lack a lipid envelope, such as human parvovirus B19 and hepatitis A, by their products.

Haemophilia C (factor XI deficiency)

Factor XI deficiency[29] is sometimes know as haemophilia C, despite its different mode of inheritance and clinical features. It is an autosomal recessive condition, particularly common in Ashkenazi Jews. Homozygotes usually have factor XI concentrations less than 4% whereas heterozygotes have a wide range of concentrations (between 15 and 65%), but the bleeding diathesis may not correlate well with factor concentrations. Factor XI has a long half-life and replacement therapy may be required only infrequently after operation. A plasma-derived, virally inactivated factor XI concentrate is available for use but is recognized to be thrombogenic in some individuals. Where factor XI is used, the target concentration should not exceed 70% for this reason. Fresh-frozen plasma contains adequate amounts of factor XI[46], and now that this product is available in a virally inactivated form some clinicians prefer to use it to minimize thrombotic complications.

Table 3 Plasma levels of factor VIII to achieve haemostasis

Clinical indication	Plasma factor VIII target (IU dl^{-1})	Dose of factor VIII (IU kg^{-1})
Early haemarthrosis or muscle bleed	15–20	8–10
Minor trauma or more severe bleeding	30–50	15–25
Surgery, major trauma or head injury	80–120	40–60

Von Willebrand's disease

The basic defect in this condition is abnormal production of von Willebrand factor (vWF), a long protein monomer produced from the Weible Palade bodies of endothelial cells and from the alpha granules of platelets. vWF functions primarily in platelet adhesion to the subendothelial layers at high shear rates and, in addition, acts as a carrier molecule for factor VIII coagulant protein in the circulation. Hence, the clinical presentation is characterized by mucosal bleeding and easy bruising in association with a prolonged bleeding time in the majority of kindreds, where inheritance is autosomal dominant. It is the commonest of the inherited bleeding disorders, and it has been suggested that it might be present in as many as 20% of women with menorrhagia. Very rarely, the condition occurs in a severe form with

autosomal recessive inheritance, very low concentrations of vWF and clinical features more like classical haemophilia, spontaneous haemarthroses occurring as well as mucosal bleeding.

Von Willebrand's disease is diagnosed[48] by measuring factor VIII coagulant protein (VIIIc), vWF antigen (vWFAg) and platelet activity as an estimate of binding to platelet glycoprotein with ristocetin as cofactor (vWRiCof), all of which will be reduced to 40% or less, giving rise to a prolonged bleeding time in the presence of a normal platelet count. These assays are, however, measuring labile factors which are influenced by stress and the results may therefore be variable and require repetition to confirm the diagnosis.

It is usually possible to avoid the use of blood components to control haemorrhage in the majority of cases of von Willebrand's disease. The antifibrinolytic agent tranexamic acid reduces minor bleeding, e.g. menorrhagia or epistaxis, and is prescribed in the postoperative period. DDAVP administered 90 min before operation at a dose of 0.3 μg kg^{-1} may be expected to increase concentrations of vWFAg and factor VIII coagulant protein to normal (>100 IU ml^{-1}) in the majority who have a quantitative defect of vWFAg. Although further doses may be given postoperatively, the effect is maximal on first administration of DDAVP in any treatment episode as tachyphylaxis is well recognized. In a small proportion of cases, namely those with a qualitative defect of vWFAg or with the more severe autosomal recessive type, a plasma product will be required to supplement vWFAg and VIIIc together. Haemate P (Centeon) and 8Y (BPL) are two intermediate-purity factor VIII concentrates which fulfil these criteria and are licensed for use in the UK.

Inherited platelet disorders

These are uncommon conditions. Inherited thrombocytopenia of clinical significance will usually be diagnosed in childhood and platelet concentrates are required to support surgery. The better-defined thrombocytopathias (platelet function defects) are also very rare.

Glanzmann's disease

Glanzmann's thrombaesthenia is characterized by the absence of platelet glycoprotein II_b/III_a, which binds fibrinogen and is the site of the platelet-specific HPA 1a antigen. Platelet transfusion[35] in patients with Glanzmann's thrombaesthenia is therefore associated with the development of anti-HPA 1a antibodies, necessitating the selection of donors lacking this antigen. Sometimes, HLA selection may be required in addition.

Bernard–Soulier disease

This is associated with a defect of platelet binding to collagen, demonstrated by absent aggregation on exposure to ristocetin. Glycoprotein I_b/IX, which is the platelet-binding site for collagen, is not, however, associated with a platelet-specific antigen site, and patients may usually, therefore, be repeatedly transfused with platelet concentrate[35] without acquiring specific antibodies.

Platelet storage pool defects

Far more common, but with less well-defined causes, are the platelet storage pool defects, many of which are reversed by administration of DDAVP. Where this agent fails to correct a prolonged bleeding time, transfusion with platelet concentrate will be required to cover surgery. Since the introduction of universal leukodepletion of platelet concentrate in the UK in 1998, the incidence of febrile transfusion reactions and development of HLA antibodies has been significantly reduced.[8 34]

Acquired disorders of haemostasis

Consumptive coagulopathies

The consumptive coagulopathies are a spectrum of disorders characterized by inappropriate and widespread small vessel thrombosis, associated with generalized bleeding as a result of the consumption of coagulation factors and excessive fibrinolysis. Very often, a microangiopathic haemolytic anaemia ensues as red cells are damaged passing through blood vessels distorted by thrombosis. Although several distinct syndromes are described, the first line of management is to diagnose and treat the underlying cause.

Disseminated intravascular coagulation (DIC)

DIC is the most common consumptive coagulopathy, often with a prodromal thrombocytopenia giving way to hypofibrinogenaemia as a result of excessive fibrinolysis, the latter demonstrated by increased fibrin(ogen) degradation products and D-dimers. In the absence of sepsis or obstetric causes, extensive endothelial damage with collagen exposure may initiate the process. The main causes of DIC are listed in Table 4.

In this condition, there is rarely an underlying immune cause, and transfusion support should be guided by clinical signs and coagulation results to include platelet concentrate,[35] fresh frozen plasma,[46 52] cryoprecipitate (as a source of fibrinogen) and red cells. During 1999, component preparation was modified to ensure that all red cells, as well as platelet concentrate produced within the UK, are leukodepleted at source to minimize febrile reactions and HLA sensitization. A number of other agents have been advocated in certain specific situations.[38] Antithrombin III[12] concentrate may reverse the DIC process in septicaemia, with notable success in meningococcal infection. It has been suggested that protein C concentrate[42] may be equally effective in paediatric practice, but comparative data are difficult to evaluate in view of the extensive therapeutic support which is required to achieve a successful outcome in such patients. Where platelet activation is thought to be the

Table 4 Aetiology of disseminated intravascular coagulation

Condition	Examples
Infection	Septicaemia, e.g. meningococcaemia
	Viraemia
	Protozoa, e.g. malaria
Malignancy	Metastatic carcinoma
	Haematological (especially acute promyelocytic leukaemia)
Obstetric disorders	Septic abortion
	Placental abruption
	Pre-eclampsia (pregnancy-induced hypertension)
	Amniotic fluid embolism
	Placenta praevia
Shock	Trauma
	Burns
	Heat stroke
Liver disease	Cirrhosis
	Acute hepatic necrosis
Transplantation	Tissue necrosis
Extracorporeal circulation	Cardiopulmonary by pass
Intravascular haemolysis	ABO incompatible blood transfusion
	Snakebite

Table 5 Classification of autoimmune thrombocytopenia

A	Idiopathic (primary)
	A diagnosis of exclusion of secondary causes
B	Secondary
	Drug-induced
	Drug-dependent
	Drug-independent
	Autoimmune systemic disorders
	Organ-specific, e.g. thyroid
	Haematological, e.g. Evans syndrome
	Generalized, e.g. systemic lupus erythematosus
	Malignant disease
	Non-Hodgkin's lymphoma
	Chronic lymphocytic leukaemia
	Carcinoma
	Postinfective
	Childhood virus
	Immunodeficiency
	Post-transplant
	Chemotherapy, radiotherapy
	HIV

primary cause, prostacyclin has been tried. Aprotonin may be helpful where the original problem is thought to be fibrinolysis. The use of antifibrinolytic agents may, however, be complicated by the formation of permanent clot in undesirable sites such as small renal blood vessels.

The prescription of heparin is controversial,[13] with reports of benefit in amniotic fluid embolism,[23] but is a brave course to take in the haemorrhagic patient. In acute promyelocytic leukaemia, however, where disseminated intravascular coagulation is a frequent association, heparin and platelet support may be used to advantage to cover remission induction[1 22] and sometimes an antifibrinolytic agent may be helpful, depending on the coagulation profile.

Microangiopathic haemolytic anaemias

Less common are the microangiopathies, which are thought to be immune in origin and in which platelet transfusion is contraindicated.

Thrombotic thrombocytopenic purpura (TTP). In TTP, there is a predominantly neurological deficit caused by thrombosis in small cerebral vessels in association with fever and thrombocytopenia, and there is often evidence of an underlying immune disorder. Recently, it has been shown that there is an increase in very large molecular weight multimers of vWF as a result of the formation of an antibody to their cleaving metalloprotease.

Haemolytic uraemic syndrome (HUS). By contrast, HUS features renal dysfunction with thrombocytopenia, often after an infection, particularly with enteric pathogens which produce a verotoxin in children.

In both HUS and TTP, thrombocytopenia is the predominant haematological feature, in association with microangiopathic haemolysis. The treatment for both conditions is total plasma exchange ($1\frac{1}{2}$ volumes), replacing with cryoprecipitate supernatant[2 39] plasma, which is deficient in high molecular weight von Willebrand multimers. Platelet transfusion must be avoided.

The immune thrombocytopenias

The main causes of autoimmune thrombocytopenias are described in Table 5. Their prognosis and management varies according to their causative antibody and presentation.[15 16 25] An acute thrombocytopenia caused by IgM antibodies is the commonest form in childhood, commonly following a viral illness and usually recovering spontaneously with no need for therapeutic intervention.

Adults, by contrast, are more likely to acquire an IgG-mediated disorder which runs a chronic course and requires immunosuppressant therapy. Although some individuals remit on steroids, many relapse when treatment is stopped, and in this group splenectomy offers a 50% chance of cure. The platelet count may be improved in preparation for surgery using a course of i.v. immunoglobulins at a dose of 0.4 mg kg^{-1} daily for 5 days, a target platelet count of 80–100 $\times$ 10^9 $litre^{-1}$ being considered adequate to secure haemostasis at operation. The introduction of laparoscopic technology to perform splenectomy has reduced the morbidity of the procedure significantly.[3]

The permanent risk of overwhelming postsplenectomy infection remains. Vaccination against pneumococcal pneumonia should be administered before operation in the form of Pneumovax and pneumococcal antibodies quantitated every 5–10 yr, with booster immunization as necessary. To obtain an optimal response, immunization should start 2–3 months before surgery. In addition, vaccination against *Haemophilus influenzae* B and the meningococcal strains A and C should be provided, with a recommendation for lifelong oral prophylaxis against encapsulated organisms with daily penicillin V or erythro-

Table 6 Causes of maternal thrombocytopenia in pregnancy

Spurious
'Benign' gestational thrombocytopenia of pregnancy
Autoimmune thrombocytopenia
Idiopathic
Drug-related
HIV–associated
Pre-eclampsia; HELLP syndrome
Disseminated intravascular coagulation (DIC)
Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenia purpura (TTP)
Severe folate deficiency
Others (rare)
Congenital, e.g. May–Hegglin, Bernard–Soulier
Hypersplenism
Coincidental marrow disease

mycin.[33] In view of the rebound thrombocytosis which usually occurs immediately after operation, such individuals are at increased risk of venous thromboembolism in the peri-operative period and require adequate anticoagulant prophylaxis until they are fully mobile.

Unfortunately, about one-quarter of cases of chronic thrombocytopenia fail to respond to these measures and must then be managed on the basis of their haemorrhagic risk. Other treatment strategies include alternative immunosuppressants, e.g. azathioprine, cyclosporin, vincristine and synthetic hormones, e.g. danazol.

Thrombocytopenia in pregnancy

Special consideration must be given to the management of thrombocytopenia in pregnancy.[32] Maternal thrombocytopenia is a frequent occurrence in pregnancy, the causes of which are set out in Table 6. The platelet count tends to fall in a normal pregnancy. Although mild thrombocytopenia ($120–150 \times 10^9$ litre^{-1}) is not uncommon, it is important that more serious underlying disease is excluded.

Having eliminated the apparent thrombocytopenia associated with platelet clumping in the anticoagulant EDTA, the commonest cause is 'benign' gestational thrombocytopenia, which occurs in up to 7% of pregnancies. The platelet count rarely falls below 80×10^9 litre^{-1} and no intervention is, therefore, necessary as the condition is reversible after delivery.

When autoimmune thrombocytopenia is present in pregnancy, management is directed at maintaining a maternal platelet count above 50×10^9 litre^{-1} to minimize peripartum haemorrhage and prevent spontaneous fetal haemorrhage. Evidence of associated autoimmune disorders, such as the antiphospholipid syndrome, should be sought. In many cases, no intervention is necessary and vaginal delivery proceeds uneventfully, although epidural anaesthesia is contraindicated if the platelet count falls below 80×10^9 litre^{-1}. If the platelet count falls below 50×10^9 litre^{-1}, specific measures are required to prevent bleeding at delivery. Treatment options are corticosteroids and high-dose i.v. immunoglobulin (0.4 g kg^{-1} daily for 5 days) Where these modalities fail, consideration should be given to high-dose methylprednisolone and other immunosuppressants, such as azathioprine. Splenectomy should be a last resort in the presence of a gravid uterus, but is best performed before 28 weeks with the support of platelet transfusion.

The neonates of such severely affected mothers require careful surveillance for the first few days after delivery, as the nadir in the platelet count occurs from the second to the fifth day of postnatal life as the splenic circulation is established.

The thrombocytopenia and disseminated intravascular coagulation of obstetric complications such as pre-eclampsia will require specific transfusion support in line with the results of serial monitoring of the coagulation profile, with urgent delivery of the fetus to secure early resolution. More rarely, recovery may be delayed until a few days after the baby is delivered in the presence of maternal haemolysis with elevated liver enzymes and low platelets (HELLP) syndrome.

Thrombocytopenia as a feature of thrombotic thrombocytopenic purpura and the haemolytic uraemic syndrome is a rare event in pregnancy and the post-partum period. Additional features include microangiopathic haemolytic anaemia with fluctuating neurological signs and deteriorating renal function. Evidence of DIC is absent and prompt delivery does not expedite clinical resolution. Furthermore, platelet transfusion is contraindicated and urgent plasma exchange is required, replacing with fresh frozen plasma.

Massive transfusion

Massive transfusion involves the replacement of circulating blood volume within 24 h and often much more quickly. Stored red cells are deficient in functional platelets and plasma reduction effectively removes coagulation factors. Transfused red cells serve to dilute out the patient's native coagulation reserves.[7] These effects are exacerbated by the infusion of dextrans and/or starch. Specific transfusion of coagulation factors in the form of fresh frozen plasma[52] and platelet concentrate[35] should be guided by the results of the coagulation profile, which must be repeated until haemostasis is achieved.

Each unit of blood is collected from the donor in 63 ml of anticoagulant (citrate phosphate dextrose with adenine), and higher volumes transfused lead to citrate toxicity with associated hypocalcaemia. In emergency situations, when blood is transfused rapidly, cooled red cells may also contribute to the patient's falling pH. Care must be exercised in the use of blood-warmers and pumps to ensure their proper function, in order to avoid haemolysis of red cells for transfusion. Potassium toxicity rarely presents problems in this situation except in neonates.

Extracorporeal circuits

Widely used for many years in cardiopulmonary bypass procedures, other extracorporeal techniques, such as intraoperative cell salvage, may now contribute to the

support of various operative procedures. When platelets are exposed to large areas of inert material, some are retained there, rendering the patient thrombocytopenic. Reduced temperatures inhibit the production of thromboxane A_2 in some platelets, while others aggregate spontaneously and prematurely. Those platelets which do return to the patient's circulation may thus have been injured on their journey, for early sequestration in the spleen. For these reasons, the bleeding patient may benefit from platelet transfusion, irrespective of the postoperative platelet count after bypass procedures.

Anticoagulation administered to facilitate cardiopulmonary bypass procedures may also be associated with postoperative bleeding. Heparin is reversed by protamine sulphate,[9] which, in excess, gives rise to a consumptive coagulopathy. If neutralization is incomplete, active heparin may reappear in the circulation 2–6 h after operation as it is released from heparin–protamine complexes in the extravascular compartment.

Acquired inhibitors of coagulant factors

Whilst inhibitors occur quite frequently as IgG antibodies directed against transfused factor VIII concentrate, the occurrence of antibodies to coagulation factors *de novo* is a much rarer event.[20] These are diagnosed in the presence of a prolonged time in a coagulation screen which fails to be corrected on addition of normal plasma. Commonly associated with autoimmune disorders, drug reactions or the post-partum period, patients with inhibitors usually present with severe mucosal bleeding, whereas spontaneous haemarthrosis is uncommon. In the postoperative period, this may lead to wound haematoma and/or secondary haemorrhage. The principles of management are threefold: to treat any underlying cause; to restore the deficient coagulation factor; and to block the formation of its inhibitor. In acquired haemophilia, agents prescribed to achieve haemostasis include large doses of factor VIII concentrate of human origin and porcine factor VIII. When the titre of factor VIII inhibitor exceeds 100 units per millilitre, specific factor VIII concentrate is no longer effective. Attempts may then be made to secure haemostasis by bypassing factor VIII, using partly activated mixtures of vitamin K-dependent clotting factors (II, VII, 1X and X), although there is an associated thrombotic risk.

Such products include intermediate purity factor IX (9A, BPL), FEIBA (factor eight bypassing activity) (Immuno) and Autoplex (Baxter). Recombinant activated factor VII (rVIIa) may be effective when these plasma-derived products fail. Immunosuppression should be prescribed simultaneously, as high-dose steroids, i.v. immunoglobulin or alkylating agents. Where inhibitors arise in response to transfusion of factor concentrate, the relative risks and benefits must be considered carefully before any operative procedure is planned. Every effort must be made to suppress inhibitor formation before elective surgery is contemplated.

More recently, factor V inhibitors have been described following the application of topical fibrin glue and thrombin.

Intermediate coagulation disorders

These disorders are characterized by an inappropriate predisposition to both bleeding and clotting. Their pathology is usually associated with failure of one or more major organs or a multisystem disease process with variable expression.

Renal disease

In renal failure, a decrease in erythropoietin production gives rise to anaemia with a falling haematocrit. Together with acquired disorders of platelet adhesion and a platelet storage pool defect,[30] this leads to an increased bleeding time, which may sometimes be corrected by DDAVP.[31] The anaemia may be improved preoperatively using erythropoietin, with iron supplements as appropriate.[50]

By contrast, secondary polycythaemia as a result of renal disease is associated with a raised haematocrit and increased risk of thrombosis.

Liver disease

The liver is the production site of the majority of coagulation factors, hence disturbance of liver function may lead to a tendency to bleeding. Where cirrhosis ensues, disturbance of liver architecture predisposes[5] to a chronic consumptive coagulopathy.[10] If this is then complicated by portal hypertension, splenic sequestration contributes to the thrombocytopenia as another source of bleeding. Ascitic fluid produced in cirrhosis has been shown to contain procoagulants, including tissue factor, factor X activator, collagen and endotoxin, which predispose to thrombosis after shunting.

Systemic lupus erythematosus

Two major coagulation problems occur within the clinical spectrum of systemic lupus erythematosus. A common association is immune thrombocytopenia; the bleeding diathesis associated with this problem is discussed above. Systemic lupus erythematosus in some individuals is also associated with the production of an antibody to glycoprotein Ib, found on the platelet membrane. This may give rise to an antiphospholipid syndrome (APS), an acquired procoagulant state characterized by recurrent venous and arterial thromboembolism.[18] Cerebral episodes present a particular problem in APS, and recurrent miscarriage is a common presentation in young women with this condition. The antibody, which is known as the lupus anticoagulant, is associated with a prolonged activated partial thromboplastin time which fails to correct with normal plasma, indicating the presence of an inhibitor.

Anticardiolipin antibodies are also increased. Long-term oral anticoagulant therapy is prescribed to control symptoms. Successful outcome of pregnancy has been achieved with the prescription of aspirin and low molecular weight heparin prophylaxis. Clearly, these patients present a very high risk of thrombosis in the peri-operative period and are best managed with therapeutic doses of i.v. unfractionated heparin.

Haematological malignancy

Disseminated intravascular coagulation in acute promyelocytic leukaemia has been discussed already. Far more common are the myeloproliferative disorders, which are caused by excessive activity of the pluripotential stem cell or lack of negative feedback in its production and differentiation. Diseases in this group include polycythaemia vera, chronic granulocytic leukaemia, essential thrombocytosis and myelofibrosis. Their course is chronic and often associated with a thrombocytosis. Although this creates an increased risk of thrombosis in the peri-operative period, necessitating anticoagulant prophylaxis, the abnormal platelets produced by the defective stem cells may not function normally in response to the blood loss of surgery. Every effort should be made to restore the blood count parameters to normal before elective procedures, but abnormal bleeding, even in the presence of a normal or raised platelet count, may be controlled by transfusion of platelet concentrate[35] in such patients.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (type 2) is a disorder in which a falling platelet count occurs in association with a progressive thrombotic tendency, which affects large vessels, both arterial and venous.[11 24] More than half of those affected sustain limb amputation and the mortality is high. The thrombocytopenia is caused by a specific antibody to platelet factor 4 which promotes platelet aggregation to initiate thrombosis. It usually occurs as an acquired primary immune state between 5 and 10 days after heparin therapy is initiated, more commonly after therapeutic doses of the unfractionated drug than low molecular weight heparin.[49] It may occur before 5 days as a secondary response on inadvertent re-exposure to heparin. Although a number of antibody detection tests have been set up, the diagnosis is essentially clinical and must be followed by immediate withdrawal of heparin and anticoagulation with a heparinoid such as danaparoid or lepirudin, as parenteral therapy, to cover the introduction of oral coumarins. Should the same patient require surgery in the future, heparin must be avoided in favour of the heparinoids described above.[17]

The hypercoagulable state: hereditary thrombophilia

Over the last 20 yr, a large amount of information has accumulated about factors contributing to a hypercoagulable state.[27 37] Although many of these are associated with lifestyle risk factors such as obesity, immobility and smoking, or prothrombotic states such as malignancy, increased viscosity and pregnancy, there are a number of hereditary factors the presence of which places particular families at risk. Genetic risk factors recognized in the aetiology of venous thromboembolism are given in Table 7. The risks of venous thromboembolism in the peri-operative period are well recognized and those with heritable thrombophilia will benefit from enhanced anticoagulant prophylaxis. Antithrombin III, protein C and protein S deficiencies were first identified for their prothrombotic significance, since these proteins usually act as inhibitors of the formation of the 'tenase' complex in coagulation. Antithrombin III deficiency is the least common but the most serious. Specific concentrates of both antithrombin III and protein C are available for transfusion to cover elective surgical procedures.

Table 7 Genetic risk factors for venous thromboembolism

Anticoagulant deficiency or defect	Antithrombin (formerly antithrombin III)
	Protein C
	Protein S
Abnormal coagulant protein	Factor V Leiden
	Prothrombin gene mutation (20210)
	Dysfibrinogen
Increased procoagulant	ProthrombinFactor VIII
Abnormal metabolism	Hyperhomocysteinaemia

More recently, it was recognized that some individuals with adequate amounts of protein C antigen appear to have an activated protein C resistance which prevents protein C from acting as an inhibitor of coagulation *in vitro*. In many cases, this is caused by the presence of a variant of one of the coagulant proteins, factor V, known as factor V Leiden, which is mutated at the site for protein C interaction.[4] This is present in 5% of the population but more frequently in those with venous thromboembolism. Similarly, a variant which impairs control of the 'prothrombinase' complex is programmed by the prothrombin gene mutation 20210.[36] This occurs in 2% of the population but more frequently in those with venous thromboembolism, and is, with the factor V Leiden gene mutation, an additive risk factor.

More recently, a clear relationship has been established between arterial thrombosis and hyperhomocysteinaemia,[43] the latter being common in individuals with a variant of the enzyme methylene tetrahydrofolate reductase, particularly in the homozygous state, the prevalence being approximately 12%.[14]

The discrepancy between recorded thrombosis and the prevalence of these genetic variants in the general population indicates that, in most cases, other factors play a part in their causation. In terms of management, therefore, treatment is directed at the history of clinical events rather than the identification of isolated risk factors. Although the

Table 8 Comparison of properties of unfractionated heparin and low molecular weight heparin

Property	Unfractionated heparin	Low molecular weight heparin
Mean molecular weight (Raye)	15 (4–30) kDa	4.5 (2–10) kDa
Saccharide units (mean)	40–50	13–22
Relative activity anti-X^a/anti II_a	1:1	3:1 (2:1–4:1)
Inhibits platelet function	Yes	No
Bioavailability at low dose	50%	100%
Elimination	Hepatic and renal	Renal
Half-life of anti X^a activity		
Intravenously	1 h	2 h
Subcutaneously	2 h	4 h
Monitoring	Yes	No (except in renal failure and pregnancy)
Frequency of heparin-induced thrombocytopenia	High	Low
Osteoporosis on prolonged therapy	Yes	Yes
Risk of haemorrhage	Present	Reduced

presence of additional prothrombotic markers may be considered in the risk assessment used to plan anticoagulant prophylaxis in the peri-operative period, this rarely influences decisions about the prescription of long-term oral anticoagulant therapy. A first episode of venous thromboembolism is treated with a discrete course of anticoagulant therapy followed by thrombophilia screening a few weeks after the end of treatment. Only after a second spontaneous event is it usual to recommend life-long therapy.[51]

Anticoagulant management in the peri-operative period

Increasing numbers of patients now receive oral anticoagulant therapy to reduce their risk of stroke from atrial fibrillation and other cardiac disorders.[51] Minor surgery, including dental extraction and endoscopy with biopsy, may be undertaken safely with an international normalised ratio of 2.5 or less. Many anticoagulant patients may have coumarin stopped for a few days without harm.

There remain two major risk groups who will require conversion to i.v. unfractionated heparin in the peri-operative period to maintain therapeutic anticoagulation in the absence of postoperative bleeding.[21,26] These are patients with mechanical cardiac valve prostheses[45] and those with a history of acute venous thromboembolism within the previous 4 weeks or during a current pregnancy. The heparin must be stopped 6 h before the operation and restart 12 h after operation, and oral coumarin should be reintroduced as soon as possible thereafter.[26] Epidural anaesthesia is best avoided for those on therapeutic heparin.[6]

Even in the absence of any known thrombophilia markers, surgical patients are at increased risk of venous thromboembolism as a result of their immobility and the postoperative inflammatory response.[40,44] All should be assessed for their individual risk in relation to the procedure planned, and advised about the importance of leg exercise and early mobilization. Appropriate antiembolism hosiery should be fitted. Anticoagulant prophylaxis with subcutaneous unfractionated heparin will cover moderate- and high-risk surgery, including operations on pelvic sites and arthroplasty, but very high-risk patients may benefit from a prophylactic dose of a low molecular weight heparin. Such prophylaxis is not usually associated with increased bleeding in the peri-operative period, but should not be prescribed for neurosurgical procedures.

In recent years, a number of low molecular weight heparins (LMWH) have been produced with specific anti-Xa activity.[19] Administered by the subcutaneous route, they are as effective as i.v. unfractionated heparin (UFH) in treating acute venous thromboembolism.[28] The comparative properties of LMWH and UFH are described in Table 8. Although all are licensed in the UK for deep venous thrombosis, only one LMWH (tinzaparin) has a licence recommendation for the treatment of pulmonary embolism.[41] In most cases, their use requires only monitoring of the platelet count to exclude heparin-induced thrombocytopenia, although anti-Xa concentrations require checking in patients with renal failure and in the critically ill. It has been suggested that haemorrhagic complications are less frequent with LMWH than UFH because of their specificity of action.[23]

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