Haemostasis in Surgery

Nadey S. Hakim • Ruben Canelo *editors*

Imperial College Press

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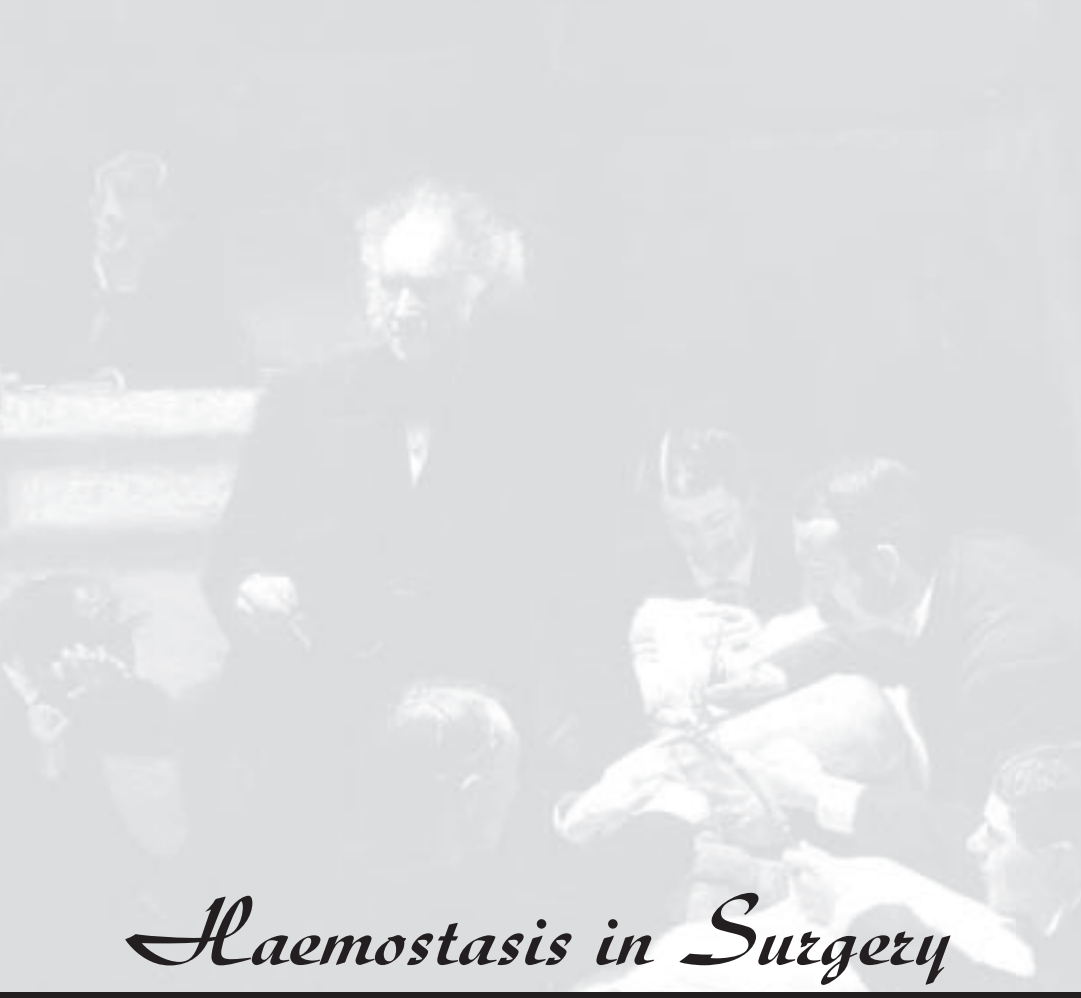

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To my wife Nicole and my children
Alexandra, David, Andrea and Gabriella
for their encouragement, support, understanding
and patience during the preparation
of this book, **NH**

To my son Thomas, **RC**

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Contents

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Foreword

It is significant that the first medical description of the clinical and genetic features of haemophilia was by the "father of surgery" Abu al-Qasim Khalaf bin 'Abbas el-Zahrawi (940?–1031 C.E.), so called for his extensive original descriptions of operative techniques and instrumentation. Characteristically he also described a method for stopping bleeding in haemophilia by local pressure and cauterisation, which he had witnessed.

Surgeons have always been concerned with bleeding and haemostasis since the first obvious side effect of any surgical intervention is blood loss. Means to control and limit bleeding during and after surgery remain a topic central to modern practice of the speciality, in which larger operative fields need to be kept "dry" or in which very small areas under the operating microscope need to be clearly seen without obscuring blood. Hence it may be surprising that, prior to the present volume, no other work has been published exclusively devoted to this topic.

Our present understanding of the highly complex physiological system that has evolved to keep blood fluid within the circulation and yet allow for it to rapidly form a leak proof plug at the site of any injury is now fairly mature. Yet there remain circumstances in which bleeding continues in spite of adequate amounts of platelets and of all

the known coagulation proteins. New reagents, such as recombinant factor VIIa, are now under trial that may offer help to the hard pressed surgeon dealing with massive trauma of difficult re-operations where such bleeding occurs. Thus, although our knowledge of all the details of haemostasis *in situ* may still be incomplete, practical help is at hand as described within these pages.

Hakim and Canelo have marshalled a team of experts to consider this vital topic in each of the major areas of surgical practice, and have thus brought together a vast body of experience and analysis to address the ever-present threat of incontrolled blood loss or its obverse unwanted thrombosis during and after surgery.

I recommend this volume to all who have to deal with surgical bleeding both as a general educational reference and as a source of specific advice in the multitude of situations where bleeding or thrombosis may be encountered in surgical practice.

Edward G. D. Tuddenham
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Pathophysiological Aspects of Coagulation

Abdul Shlebak

SECTION I: NORMAL HAEMOSTASIS

A) Introduction

Haemostasis is a host defence mechanism that protects the integrity of the vascular system after tissue injury. It is responsible for minimising blood loss. It is critical that formation of blood clot in response to a breach in the vascular endothelium occurs rapidly. Systemic activation of the coagulation cascade or extensive local extension of thrombosis resulting in vascular occlusion, however, should not occur. Immediate vasoconstriction of the injured vessel and reflex constriction of adjacent small arteries and arterioles are responsible for an initial slowing of blood flow to the injured area (Fig. 1). The reduced blood flow enables contact activation of platelets and coagulation factors. The vasoactive amines and thromboxane A_2 from platelets and the fibrinopeptides produced during fibrin formation

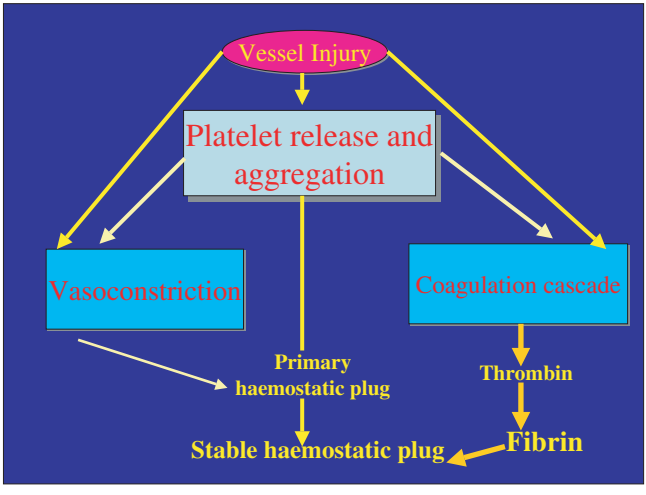


Fig. 1 Scheme of primary haemostatic function.

may also have vasoconstrictive activity.[1] Thrombin generated at the site of injury converts soluble fibrinogen into fibrin and potentiates platelet aggregation and secretion. Thrombin also activates factor XI that amplifies the intrinsic pathway activity. Furthermore, it activates factor XIII that covalently cross-links the fibrin meshwork. A meshwork of fibrin anchors and extends the platelet plug. The fibrin component increases as the fused platelets autolyse, and after a few hours the entire haemostatic plug is transformed into a solid mass of cross-linked fibrin.[2] During the same time frame, the plug begins to lyse due to the incorporation of plasminogen and tissue plasminogen-activator (t-PA) in the plug, resulting in plasmin generation.[3]

Role of endothelium and subendothelium

The active role of "endothelial cells" in preserving vascular integrity is well-established. This cell provides the basement membrane, collagen, elastin, and fibronectin of the subendothelial connective tissue. Loss of or damage to the endothelial lining results in both haemorrhage and activation of the coagulation cascade. The endothelial cell has an active role in haemostatic response, including synthesis of tissue factor, prostacyclin (Fig. 3), von Willebrand factor (vWF),

Table 1. Platelet Granule Content and Their Biological Functions

Location	Compound	Function
Alpha granule	Platelet factor 4	Neutralises heparin effect
	α-thromboglobulin	Promotes fibroblast chemotaxis
	Platelet-derived growth factor	Mitogen for fibroblast; chemotaxis for neutrophils, fibroblasts, and smooth muscle
	von Willebrand factor	Adhesion molecule; carrier for factor VIII, protecting it from proteolysis
	Thrombospondin	Promotes platelet-platelet interaction
	Fibronectin	Adhesion of platelets and fibroblasts
Dense granule	ADP	Aggregation of platelets
	ATP	Source of ATP for energy
	Serotinin	Vasoconstriction
	Calcium	Coagulation; platelet function

plasminogen activator, anti-thrombin III, and thrombomodulin (the surface protein responsible for activation of protein C). Furthermore, the endothelium provides agents that are vital to both platelet reaction and blood coagulation.[4]

Role of platelets

Platelets are derived from the cytoplasm of bone marrow megakaryocytes and are the smallest of blood cells. They are disc shaped, anucleate with a relatively complex internal structure, which reflects their specific haemostatic function (Fig. 2). Normal platelet count is $150–400 \times 10^9$/l.

The contents of both alpha and dense granules (Table 1) may be released via a system of surface-connecting tubules, during platelet activation.

Platelet reactions and primary haemostatic plug formation

Initial adherence of platelets to exposed connective tissue (Fig. 1) follows endothelial lining breakage. Biochemical pathways for the metabolism of arachidonic acid (Fig. 3) are contained in both platelets and vascular endothelial cells.[5] The platelet adhesion is

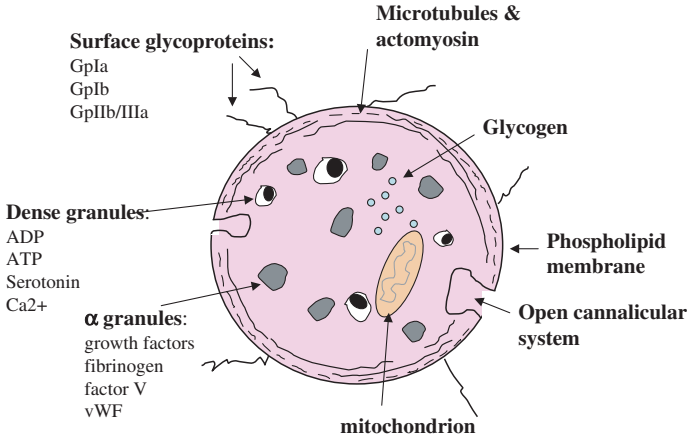


Fig. 2 Platelet electron microscopic ultrastructure (EM × 30,000).

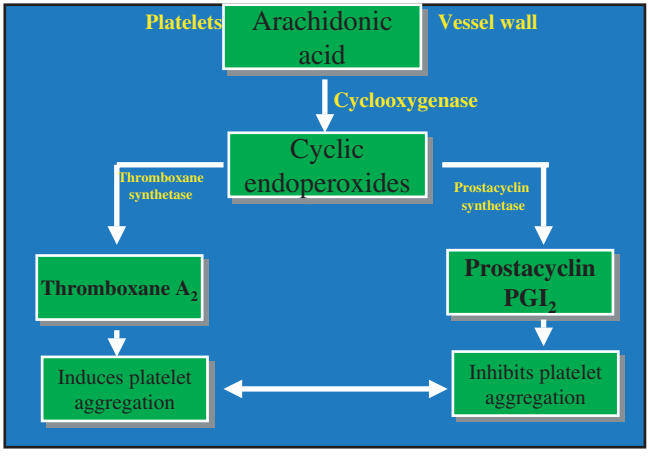


Fig. 3 Arachidonic acid metabolism in vascular endothelium and platelets.

potentiated by von Willebrand factor (vWF).[6,7] Collagen and thrombin generated at the site of injury cause the adherent platelets to release their granules, including ADP, serotonin, fibrinogen, lysosomal enzymes, and heparin-neutralising factor (PF-4). Collagen and thrombin activate platelet prostaglandin synthesis, leading to the formation of thromboxane A_2, which potentiates platelet release reactions and platelet aggregation. It is also a powerful vasoconstrictor.

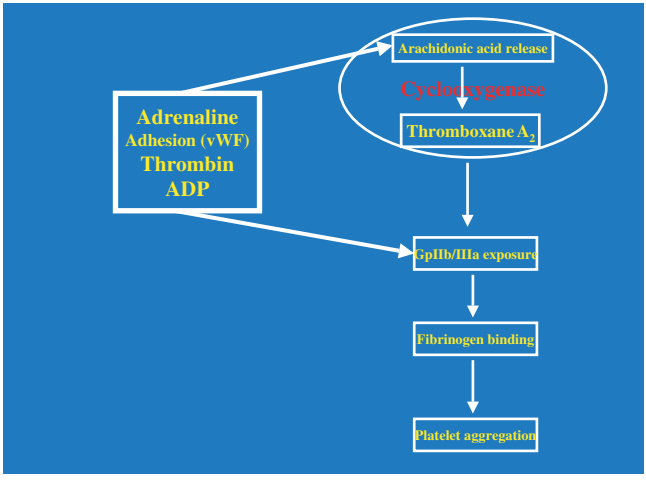


Fig. 4 Main pathways of platelet activation.

Released ADP causes platelets to swell and aggregate (Fig. 4). Additional platelets from the circulating blood are drawn to the area of injury, resulting in growth of the haemostatic plug that soon covers the exposed connective tissue. Released platelet granule enzymes, ADP, and thromboxane A2 may all contribute to the consolidation of the accumulated platelet plug. Prostacyclin, produced by endothelial and smooth muscle cells in the vessel wall adjacent to the area of damage, is important in limiting the extent of the initial platelet plug. This unstable plug produced is sufficient to provide temporary control of bleeding. Definitive haemostasis is achieved with fibrin formation by blood coagulation and with platelet-induced clot retraction.[5,7,8]

Role of circulating proteins with procoagulant, anti-coagulant, and fibrinolytic activities

Coagulation

The coagulation cascade involves sequential activation of a number of blood clotting factors, resulting in the formation of fibrin. Figures 5 and 6 show how the coagulation cascade operates *in vitro* (Fig. 5) with the classical waterfall hypothesis, whereas (Fig. 6) is thought to represent the *in vivo* process.

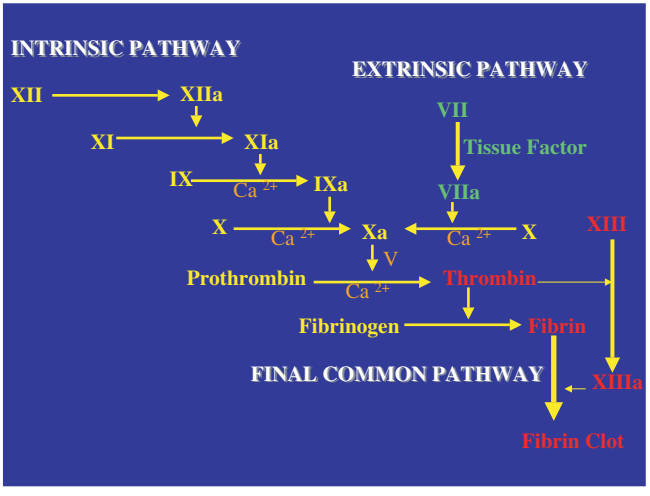


Fig. 5 Classical waterfall hypothesis of coagulation.

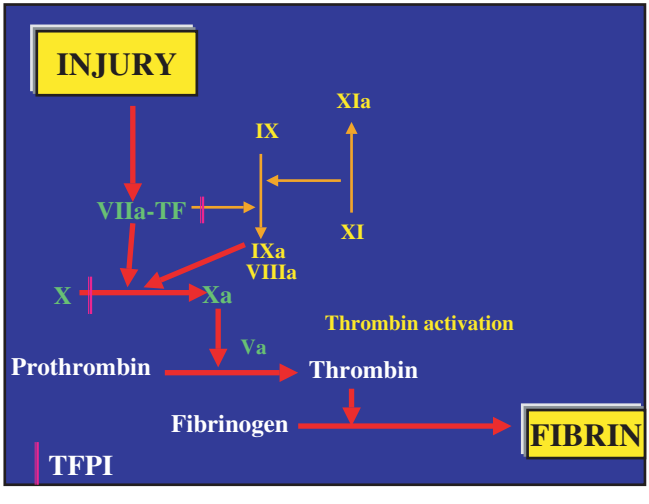


Fig. 6 The revised hypothesis of coagulation.

Conventionally, the coagulation cascade has been divided into intrinsic, extrinsic, and final common pathways. The **intrinsic pathway** ensues when the negatively charged subendothelium activates factor XII which, in turn, leads to activation of factor XI that activates

factor IX. In association with calcium and with factor VIII as a cofactor, activated factor IX activates factor X on the membrane surface provided by platelet phospholipid (platelet factor 3). The intrinsic pathway is mediated via the contact factor system; following limited activation, factor XII activates prekallikrein to kallikrein, which in turn, activates factor XII. High molecular weight kiniogen (HMWK) is a non-enzymatic accelerator of these interactions. In the **extrinsic pathway** tissue factor activates factor VII, which in turn, activates factor X both directly and indirectly via activating factor IX. The **final common pathway** is concluded when activated factor X, in association with cofactor factor V on phospholipid surface and calcium, converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin.[9,10]

In vivo versus *in vitro* coagulation: The role of factor VII-tissue factor complex (TF-VII)

Current evidence indicates that the dominant pathway for blood coagulation is via factor VII and TF, and that the contact system activation plays a little role, if any, *in vivo* coagulation. Mainly, factor VII causes activation of factor IX.[11,12] Factor XI *in vivo* is activated directly by thrombin and is important only at sites of major trauma or operation.[11–13]

Therefore, the classical waterfall hypothesis described above, fails to represent accurately *in vivo* haemostasis. This is may be demonstrated by considering the following issues. First, although patients with congenital deficiency of factor XII, prekallikrein, or HMWK have extremely prolonged aPTTs, they do not have any clinical bleeding manifestations. This clinical observation indicates that these proteins are probably not important components of blood coagulation *in vivo*. Similarly, factor XI deficiency is not always associated with bleeding and, therefore, its role is unclear. Patients with factor VII deficiency, however, bleed abnormally, although the intrinsic pathway is largely intact. Third, factor VII-tissue factor is known to activate not only factor X, but also factor IX. In the classical pathway this activation is not required. Tissue factor is a natural constituent of many non-vascular cells. Tissue factor on such cells is able to initiate blood coagulation, supporting a more central role for the TF-VII complex.[14]

The revised hypothesis of coagulation

Based on the findings of the direct activation of factor IX by factor VII-tissue factor the coagulation cascade was revised, with factor VII-TF and factor X central to the model. This model also takes into account the newly discovered feedback inhibition of factor VIIa-tissue factor produced by tissue factor pathway inhibitor (TFPI).[14,15]

The role of vitamin K in blood coagulation

In addition to protein C, protein S, and protein Z coagulation factors II, VII, IX, and X are dependent on vitamin K for their biological activation and, therefore, normal function. These are synthesised in the liver in inactive forms that cannot bind calcium ions. This ability is conferred by a post-translational modification that involves gamma carboxylation of glutamic acid residues. Vitamin K *in vivo* continuously cycles between three forms: vitamin K quinone, vitamin K hydroquinone, and vitamin K epoxide. The gamma carboxylation reaction is coupled to the conversion of vitamin K hydroquinone to the epoxide form. Therefore, in vitamin K deficiency, gamma carboxylation fails and non-carboxylated forms of factors II, VII, IX, X and protein C, protein S, and protein Z are released into the circulation. Although they are immunologically identical to the normal proteins, these proteins induced by vitamin K absence or antagonism (PIVKAs) cannot bind calcium ions. They are non-biologically competent as they cannot bind to phospholipid surfaces.[16]

Fibrinolysis

Like coagulation, fibrinolysis is a normal haemostatic response to vascular injury. The deposition of fibrin is coupled by activation of the fibrinolytic pathway (Fig. 7). Fibrinogen and fibrin are substrates for the proteolytic action of plasmin. Unlike the highly specific action of thrombin on fibrinogen, which results in the cleavage of only two pairs of small fibrinopeptides, A and B, plasmin cleaves fibrinogen and fibrin at multiple sites. This produces a variety of split (degradation) products. Plasmin is normally present in its inactive zymogen form, plasminogen, in blood, urine, and tissue fluids. Major activation of the fibrinolytic system follows the release

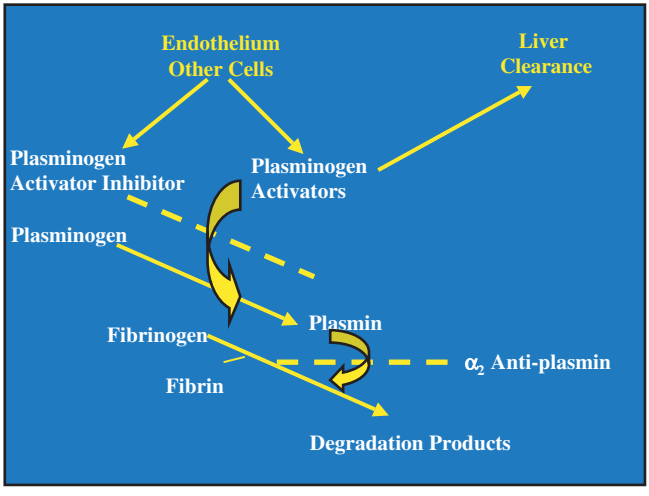


Fig. 7 Fibrinolysis.

of tissue plasminogen activator (t-PA) from endothelial cells. t-PA is a serine protease that binds to fibrin. This enhances its capacity to convert thrombus-bound plasminogen into plasmin. This fibrin dependence of t-PA action strongly localises plasmin generation by t-PA, to the fibrin clot. Release of t-PA occurs after stimuli, such as, trauma, exercise, or emotional stress. Activated protein C stimulates fibrinolysis by destroying plasmin inhibitors of t-PA. Therapeutic t-PA and urokinase are produced by recombinant DNA technology, while the fibrinolytic agent, streptokinase, is a peptide produced by haemolytic streptococci. It forms a complex with plasminogen, which converts other plasminogen molecules to plasmin. Plasmin has a wider range of activity than thrombin, hydrolysing both arginine and lysine peptide bonds in a wider range of substrates. Tissue plasminogen activator is inactivated by plasminogen activator inhibitor-1 (PAI-1). Circulating plasmin is inactivated by potent inhibitors α2-antiplasmin and α2-macroglobulin. This prevents widespread destruction of fibrinogen and other coagulation factors.[11] In addition, thrombin activatable fibrinolysis inhibitor (TAFI) plays a role in limiting the fibrinolytic activity locally. Activated protein C stimulates the release of TAFI.[12]

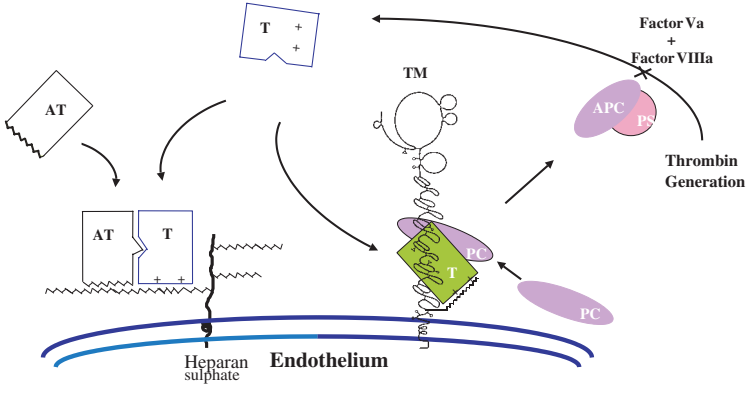
B) Haemostatic regulation

Natural anti-coagulants

The prevention of unlimited thrombin generation and, therefore, unchecked thrombosis is catalysed by the important, naturally occurring anti-coagulant proteins. These include:

(1) *Anti-thrombin*:
Anti-thrombin (AT) is a single-chain glycoprotein synthesised in the liver and the endothelium. AT is the main physiological inhibitor of activated coagulation serine proteases (Figs. 8 and 9). It inactivates thrombin, factor Xa, IXa, and XIa. Its activity is greatly accelerated (1000- to 2000-fold) by therapeutic heparin and, therefore, it is sometimes known as heparin co-factor I.[17]

(2) *Heparin co-factor II*:
This is also a single chain glycoprotein and is of liver origin. It complexes with thrombin in a 1:1 ratio, thereby inactivating it. In contrast to AT, heparin co-factor II is specific for thrombin, having no inhibitory activity against the other serine proteases. Its activity is also greatly amplified, 1000-fold, by therapeutic heparin.



Key: AT, anti-thrombin; T, thrombin; TM, thrombomodulin; PC, protein C; PS, protein S

Fig. 8 Natural anti-coagulant pathways that inhibit thrombin generation.

(3) *Protein C and Protein S pathway*:
Protein C is a vitamin K dependent factor that plays a dual role in haemostasis by inhibiting blood coagulation and stimulating fibrinolysis. Recently, it was shown to have a major anti-inflammatory role. Upon activation by thrombin in the presence of its endothelial cofactor, thrombomodulin (TM) and protein C endothelial receptor (EPCR), activated protein C inhibits the coagulation cascade by inactivating activated factors VIII and V.[18] This reduces the rate of thrombin generation (Figs. 9 and 11). Protein S is required as a non-enzymatic cofactor for protein C activity (Figs. 8 and 10). Thrombomodulin is present in tight association with vascular endothelium. Complexed thrombin

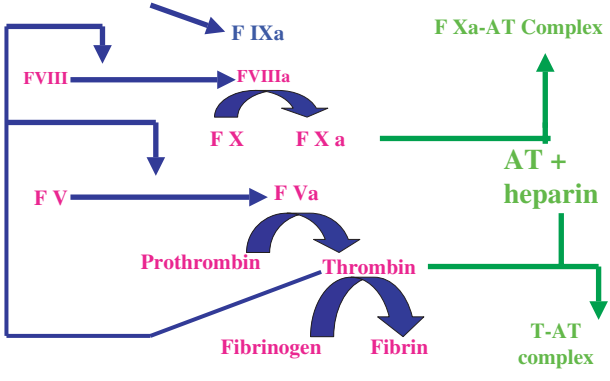


Fig. 9 Anti-thrombin pathway.

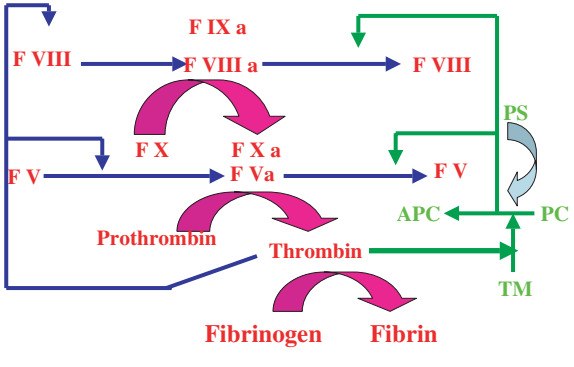


Fig. 10 PC/PS pathway.

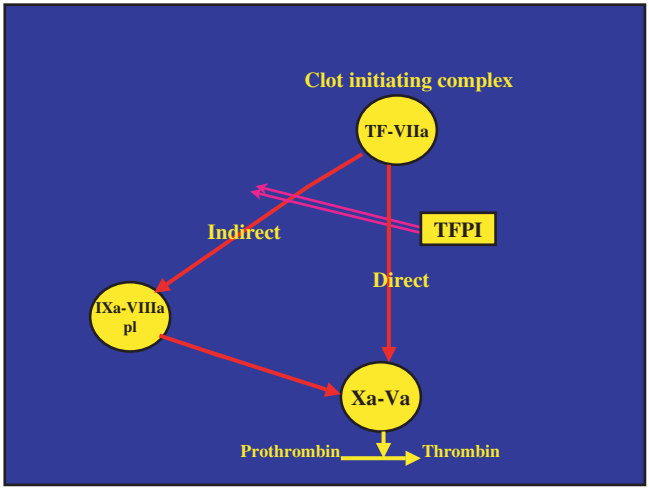


Fig. 11 TFPI.

activates protein C several thousand times faster than unbound thrombin, but does not clot fibrinogen, activate factors V and VIII, or aggregate platelets. Thrombomodulin-bound thrombin can still be inhibited by AT.

Protein S is a single chain glycoprotein synthesised in the liver and the endothelium. It is vitamin K dependent, but is not a serine protease. Activated protein C complexes with protein S and calcium ions on platelets and on the endothelial surface. The inhibitory activity of complexed protein C is greatly amplified.[18] Protein Z is also a vitamin K dependent factor, but its full function is not as yet known.

The two principle anti-coagulant pathways, known to be important in the regulation of coagulation proteinase activity are schematically represented in Figs. 8 and 9. On the left side of each diagram, is a simplified view of the coagulation cascade with its "procoagulant" feedback loops by which thrombin activates factors V and VIII. To the right, are the "anti-coagulant" pathways by which excessive activation of coagulation is prevented. These pathways involve anti-thrombin (which directly inhibits the coagulation proteins, such as, factor Xa and thrombin) and PC-PS (which inactivates factors Va and VIIIa).[18]

(4) *Tissue factor pathway inhibitor (TFPI)*:
It is an important inhibitory regulator of *in vivo* coagulation (Fig. 10). TFPI is synthesised by the endothelial cells and circulates in plasma bound to low-density lipoproteins. It is also present in platelets and bound to heparan sulphate on the endothelial surface. TFPI inhibits coagulation by binding to factor Xa-TF-VIIa complex and, therefore, inhibiting its proteloytic activity.[15,16]

It is the downregulation of tissue factor pathway activity is via a natural plasma component, tissue factor pathway inhibitor (TFPI), which halts continued direct generation of factor Xa. Therefore, continued Xa formation becomes dependent on ongoing activation of factor X by the IXa-VIIIa-phospholipid complex. Neither components of the thrombus initiating complex, TF or VIIa, can be inhibited separately (Fig. 10).[15,16]

C) Laboratory evaluation of haemostatic function

Global tests of haemostatic function

Defective haemostasis with abnormal bleeding may result from thrombocytopenia (quantitative platelet defect), platelet function disorder (qualitative platelet defect), or defective blood coagulation. Patients with a variety of vascular disorders may also suffer from a bleeding disorder. In association with the clinical picture, including family history, the haemostatsic function may be evaluable using a number of initially simple tests to assess the platelet, vessel wall, and coagulation components of haemostasis.[19]

Blood count and blood film examination

As thrombocytopenia is a common cause of abnormal bleeding, patients with suspected bleeding disorders should initially have a blood count, including platelet count and blood film examination to exclude platelet aggregation as a cause of false thrombocytopenia and confirm the presence of thrombocytopenia. The cause of thrombocytopenia may be obvious, e.g., acute leukaemia or DIC.[20]

Table 2. Screening Tests for Coagulation Disorders

Screening Test	Abnormality Indicated by Prolongation	Most Common Cause of Abnormality
Prothrombin time (PT)	Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, fibrinogen	Liver disease Warfarin therapy or other vitamin K antagonists
Activated partial thromboplastin time (APTT)	Deficiency or inhibition of one or more of the following coagulation factors: XII, XI, IX, VIII, X, V, II, fibrinogen	Haemophilia A Haemophilia B von Willebrand's disease Lupus anti-coagulants Acquired haemophilia and heparin therapy
Thrombin time (TT)	Reduction or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs	Disseminated intravascular coagulation (DIC) Heparin therapy

Screening tests of blood coagulation

These may provide an assessment of the different components of the extrinsic, intrinsic, and/or common pathway of blood coagulation (Table 2). Generally, a significant prolongation of the respective clotting tests beyond those of normal 'control' plasmas in the test system indicates a defect.

The prothrombin time (*PT*) measures the extrinsic system (factor VII) and factors common to both systems (factors X, V, prothrombin, and fibrinogen). It may be expressed as the international normalised ratio (INR). *The activated partial thromboplastin time* (*APTT*) measures the intrinsic system (factors VIII, IX, XI, and XII) in addition to factors common to both systems (factors X, V, prothrombin, and fibrinogen). *The thrombin time* (*TT*) is sensitive to abnormalities of fibrinogen (quantitative or qualitative) or to inhibition of thrombin.[19,20]

Mixing equal volumes of the test plasma with normal plasma will correct a prolonged PT or APTT due to factor deficiency. The presence of an inhibitor of coagulation is suspected when there is incomplete or no correction.[19,20]

Specialised tests that may further delineate abnormal bleeding tendencies

Assessing platelet function

When the platelet count and the blood film examination are normal, the bleeding time is performed to detect abnormal platelet function. The test measures platelet plug formation *in vivo*. Bleeding stops within 3 to 8 minutes and there is a progressive prolongation with platelet counts less than 75×10^9/l. A prolonged bleeding time is also found in patients with disorders of platelet function. The time-consuming and skill-intensive platelet aggregation studies may be of help in delineating platelet functional defects. In recent years, other less labour-intensive methods may speedily provide objective information on platelet function have become available. These include PFA-100 (platelet function analyser-100). The PFA-100 can be performed on whole blood, and would readily provide the necessary information on platelet competence.[21]

Specific assays for coagulation factors

Assays are available for measuring factors VIII, IX, XI, XII, and VWF. Factor XIII activity can be assessed by testing for clot solubility in urea. Only uncross-linked clots are soluble, suggesting factor XIII deficiency.[19,21]

Tests for fibrinolysis

Increased levels of circulating plasminogen activator may be detected by a shortened euglobulin clot lysis time. Immunological methods are available for the detection of fibrinogen and fibrin degradation products (FDPs) as well as d-dimers in serum. In patients with enhanced fibrinolysis, low levels of circulating plasminogen may be detected.[19,21] Specific assays for plasminogen, t-PA, and PAI-1 are also available.

SECTION II: VENOUS THROMBOEMBOLISM

Disregulation of normal regulatory mechanisms of haemostatic function may result in excessive haemorrhage or unchecked thrombosis.

The discussion here, will concentrate on the latter. Securing haemostasis in patients with inherited bleeding defects and those on anticoagulant therapy will be also covered in this section, but covering bleeding tendency in its entirety is outside the scope of this chapter.

A) Introduction

Venous thromboembolism (VTE) is a common and potentially lethal disease occuring at an incidence of 1 to 3 per 1000, per year.[22–27] Over 200,000 new cases occurring in the United States annually. It mainly manifests in the deep veins of the leg, but may occur at other sites, such as, the upper limbs, cerebral, intra-abdominal, liver, portal veins or retinal veins. Embolisation occurs when part(s) of the clot dislodge and are transported via the blood flow, usually through the heart to the pulmonary vasculature. VTE is more common with advancing age.

Pulmonary embolism patients face a high risk of death. Estimates of the case fatality rate, however, vary widely. Large natural history studies[25,26,28] found 12 to 25% of all events of VTE fatal, while recent trials have found much lower figures, around 1 to 3% (5 to 10% for pulmonary embolism).[28,29] Of these, 30% die within 30 days and one-fifth suffer sudden death due to pulmonary embolism. This wide range may be caused by the inclusion of thrombosis as a secondary cause of death in the studies with a high estimate. The Worcester study also showed that the case fatality rate was highly dependent on age, with a low mortality among those aged forty or less, at the time of thrombosis.[25] The post-thrombotic syndrome (PTS) leads to chronic morbidity in a substantial number of patients.[26] Despite improved prophylaxis, the incidence of venous thromboembolism has been relatively constant.

Independent risk factors for venous thromboembolism include increasing age, male gender, surgery, trauma, hospital or nursing home confinement, malignancy, neurological disease with limb paralysis, and central venous catheter/transvenous pacemaker, prior superficial vein thrombosis and varicose veins. Among women, risk factors include pregnancy, oestrogen-containing oral contraceptives, and hormone replacement therapy. About 30% of VTE surviving cases develop recurrent venous thromboembolism within 10 years.

Independent predictors for recurrence include increasing age, obesity, active cancer, and limb paralysis.[30] About 28% of cases develop venous stasis syndrome within 20 years.

Only a reduction in the incidence of venous thromboembolism can reduce sudden death due to pulmonary embolism. The incidence of venous thromboembolism has been relatively constant since about 1980. Reduction of the incidence of venous thromboembolism will require better recognition of persons at risk, improved estimates of the magnitude of risk, and avoidance of risk exposure where possible. Compared with deep vein thrombosis alone, pulmonary embolism patients have reduced survival for up to 3 months after onset. Improved therapies for pulmonary embolism are needed, especially for patients with chronic heart or lung disease. Venous thromboembolism recurs frequently. While therapeutic oral anti-coagulation prevents recurrence, venous thromboembolism sometimes begins to recur as soon as anti-coagulation is stopped. Therefore, venous thromboembolism should be viewed as a chronic disease with episodic recurrence. Recognition of venous thromboembolism as a multifactorial condition with genetic and genetic-environmental interaction has provided significant insights into the disease epidemiology and has offered the possibility of better identifying those at risk from VTE.

B) Risk factors in venous thromboembolism

Risk factors for thrombosis are usually divided into genetic and acquired. Mechanistically, they fall into three groups of causes, according to Virchow: reduced blood flow, changes in the vessel wall, and changes in the composition of the blood.[31,32] For venous thrombosis, the first (stasis) and the third group (changes in blood coagulability) appear most prominent. For arterial disease, factors that affect the vessel wall, i.e., promote atherosclerosis are most relevant. The genetic risk factors for venous thrombosis are all associated with changes in the blood composition. Acquired causes are either associated with decreased flow, i.e., immobilisation, paralysis, surgery, or plaster casts or related to hypercoagulability, such as in, the antiphospholipid antibody syndrome, pregnancy, oral contraception, or cancer. Table 3 lists the main risk factors for venous thrombosis.

Table 3. Risk Factors in VTE

Acquired	Inherited	Mixed/Unknown
Age	Factor V Leiden mutation	Hyperhomocysteinaemia
Malignancy	Prothrombin 20210A	Elevated factor VIII
Previous VTE	Protein S deficiency	Non-Leiden APC-resistance
Immobilisation	AT deficiency	Elevated factor IX
Orthopaedic surgery	Protein C deficiency	Elevated factor XI
Oral contraceptives	Dysfibrinogenaemia	Elevated levels of TAFI
Hormonal replacement therapy		
Anti-phospholipid syndrome		
Myeloproliferative disorders		

The term "thrombophilia" defines situations associated with an increased risk of VTE characterised by hypercoagulability. Inherited coagulation abnormalities predisposing to VTE, such as, deficiencies of the naturally occurring anti-coagulants anti-thrombin, protein C, and protein S and genetic mutations in coagulation factor V (factor V Leiden) and prothrombin[33–35] define inherited thrombophilia. These two mutations in coagulation factors, together with high factor VIII levels have been identified as risk factors only in the last decade, and their identification has greatly improved our understanding of the aetiology of VTE. Today, inherited thrombophilia may explain more than 50% of cases of VTE.[33–35] On the other hand, individuals with thrombophilia, particularly with the more common factor V Leiden or prothrombin mutations, frequently remain asymptomatic. This suggests that risk factors for inherited thrombophilia require interactions with other factors to elicit thrombosis. Situations of acquired thrombophilia associated with an increased risk of VTE, i.e., the presence of anti-phospholipid antibodies, cancer, surgery, trauma, prolonged immobilisation, pregnancy/puerperium, and oral contraceptive use have been known for many decades. Some of these acquired conditions, such as, surgery or pregnancy are transient, but others, such as, anti-phospholipid antibodies or cancer may persist over time.

The presence and the interactions of transient or persistent risk factors for VTE, as well as their different strengths in triggering

thrombosis must be taken into account for making decisions on primary and secondary prophylaxis of VTE with anti-thrombotic drugs. While awaiting specially designed controlled clinical trials, decisions concerning anti-thrombotic prophylaxis, particularly secondary prophylaxis, should be based on the identification of different risk profiles of individual cases.

Acquired risk factors for venous thromboembolism

Age

VTE rarely manifests before puberty, after which the annual incidence progressively increases. The estimated annual incidence of VTE is 1 per 10,000 in the young (before age 40) and 1 per 1000 among the elderly (after age 75).[22–26] Higher incidence of malignancy and frequent orthopaedic surgery in the elderly population may partially explain the high incidence. The thrombotic risk associated with age may be further excerabated by thrombophilic abnormalities as it has been shown that men heterozygous for factor V Leiden have an age-related increased risk for VTE.[34,35] Furthermore, three other studies on very elderly people (above 85 years of age and centenarians) have shown a similar prevalence of the factor V Leiden mutations among young people, with no selection effect.[34,35] In addition, there is no association between age and the plasma levels of anti-thrombin, protein C, protein S, and TFPI as observed in a study of patients over 65 years of age.[33]

Malignancy

The procoagulant activity of tumour cells or their products and the administration of chemotherapeutic drugs[36–40] account for the associated increased risk of thrombosis in cancer patients. VTE is more common with certain types of cancer, such as, pancreatic, gastrointestinal, ovarian, prostatic, or pulmonary neoplasms.[38,39] VTE usually complicates advanced malignant disease. It may also, however, be the first sign of an underlying cancer that may herald the diagnosis of cancer by several years.[41] In individuals with a first episode of idiopathic VTE, there is a 10 to 20% probability of having cancer at diagnosis or within the following 24 months.[38]

Therefore, a physical examination together with routine laboratory testing, chest radiograph, and abdominal ultrasonography should be performed in all patients aged over 40 years, presenting with idiopathic VTE. The initiation of more aggressive investigations is controversial, in the absence of any evidence of improved survival or cost effectiveness. Further investigations, such as, CT-scan of the pelvis, abdomen, and chest, however, should be performed routinely in patients aged over 25 years, presenting with idiopathic VTE. These investigations may identify an occult cancer in its early stage in approximately 10% of cases.[38,40] In addition, a thorough search for occult cancer should be carried out in patients with recurrent thrombosis involving superficial or deep veins, especially if anti-coagulant therapy has been given.

Anti-phospholipid antibodies

This is an acquired condition, sometimes associated with systemic lupus erythematosus or other autoimmune diseases in its secondary form. Lupus anti-coagulant and anti-cardiolipin antibodies together form the anti-phospholipid antibody family.[41] The prevalence of anti-phospholipid antibodies in patients with VTE ranges from 5 to 15%, while the prevalence in the general population is not well established.[42,43] Clinically, individuals with this acquired thrombophilic state may develop venous or arterial thrombosis and recurrent foetal loss. Placental insufficiency is thought to be the cause of the obstetric complications.[42,43] It has been shown that the thrombotic risk in individuals with this abnormality is increased 9-fold, and the probability of recurrence may be higher.[44]

History of venous thromboembolism

The history of previous VTE is an independent risk factor for further thrombotic events. Patients who have had VTE have an increased frequency of new episodes.[30] The malfunctioning of venous valves, which follows thrombosis of deep veins in the leg, is an important factor contributing to stasis. This, in turn, increases the risk of recurrence.[30] As the increased risk does not seem to be attributable

to known thrombophilic factors, a history of previous VTE remains an independent risk factor for recurrence.

Transient risk factors for venous thromboembolism

Surgery and major trauma

Together with malignancy, surgery is a common (and likely to be the strongest) risk factor for VTE. Orthopaedic surgery and neurosurgery are among the most thrombogenic.[45–47] The risk of deep vein thrombosis after total knee or hip replacement carried out without prophylaxis, ranges from 45 to 70%, with fatal pulmonary embolism complicating up to 3%.[48] A high risk of thrombosis is also associated with abdominal surgery, urological surgery (particularly open operations of the prostate), and gynaecological surgery.[49] The risk of thrombosis is not confined to the immediate postoperative period, but continues for several weeks.[46] Similar to surgery, major traumas, such as, head trauma, spinal injury, and pelvic fracture are frequently complicated by VTE. Nearly 60% of individuals with major trauma had deep vein thrombosis of the legs. This, in most cases, was asymptomatic.[50] Pulmonary embolism is the third most common cause of death in individuals with trauma, occurring in 2 to 22% of those who survive the first 24 hours.[50]

Pregnancy and the puerperium

Assuming that the incidence of VTE in women of fertile age is 1 per 10,000, pregnancy enhances the risk by 10-fold to up to 1.3 per 1000.[51,53] The relative risk of VTE during the puerperium, defined as the 6 weeks after delivery, is 10- to 15-fold higher than that during pregnancy.[51,52] Assuming that the duration of pregnancy is 280 days (40 weeks) and the puerperium is 42 days (6 weeks), the relative distribution of 100 venous thrombotic episodes would be 0.23 and 0.82 per day, respectively.[51] In women heterozygous for the factor V Leiden the risk of pregnancy-related VTE is 1 per 100 pregnancies and in heterozygous women with the prothrombin mutation it is 1 per 500.[52] The same risk becomes 1 per 25 pregnancies in women with homozygous factor V Leiden.[52] The reasons for increased thrombogenicity are multifactorial, including hypercoagulability and hypofibrinolysis

due to changes in blood constituents during pregnancy. Obesity and high parity are also contributory factors. The further increase of the risk during the puerperium is only explained partially by caesarean section at delivery and by procoagulant changes. Inherited thrombophilic factors are associated with an increased risk of thrombosis during pregnancy and the puerperium.[52]

Oral contraceptives and hormone replacement therapy

The increased risk of VTE associated with the use of oral contraceptives has been known since the early 1960s. In women of childbearing age, oral contraceptives are the most common transient risk factor associated with VTE. The risk of thrombosis is primarily attributed to the oestrogen dose,[53] but the type of progestogen is also an important determinant of the risk.[54] Third generation oral contraceptives, i.e., those containing desogestrel or gestodene as progestogens, are more thrombogenic than the second-generation pill, containing levonorgestrel[53,54] and are associated with 2- to 3-fold higher risk than that induced by the third generation variety. Initially, these studies attracted a lot of controversy and criticism due to referral bias, diagnostic suspicion bias, recall bias, and reporting bias.[53,54] Subsequently, it was demonstrated that all these possible biases did not influence the risks and, therefore, the estimated risks were realistic.[53] A more pronounced APC resistance has been found with the use of third generation rather than second generation oral contraceptives.[54] The synerigistic effect of oral contraceptive use in association with thrombophilia has been well-recognised, with the risk of thrombosis being increased 20-fold in women with factor V Leiden and 16-fold in those with the prothrombin gene mutation.[54] Furthermore, a more striking risk amplification between thrombophilia and oral contraceptive use (150-fold increased risk) has been observed for cerebral vein thrombosis.[55]

Compared with oral contraceptives, there have been fewer studies on the relationship between the use of post-menopausal hormone replacement therapy and VTE. The doses of oestrogen used for post-menopausal replacement are much lower than those used for contraception, and the route of administration is sometimes different

(transdermal vs. oral). Yet, several studies have shown a 2- to 4-fold increased risk of thrombosis associated with hormone replacement therapy.[56,57] Perhaps the lower risk associated with the low oestrogen dose of hormone replacement therapy is neutralised by the higher baseline risk of post-menopausal women due to their older age, in comparison with women of child-bearing age who use oral contraceptives.

Prolonged immobilisation

This refers to any circumstance that contributes to the malfunction of the leg musculature in pumping the blood upstream in the veins. Impaired blood flow is associated with an increased risk of thrombosis. Plaster casts, bed rest, limb paralysis, and prolonged air travel are examples in which stasis plays a major role in the formation of venous thrombi.[58] Studies on autopsy series of patients confined to bed for longer periods found a prevalence of VTE ranging from 15 to 80%.[47,59] Although the relative risk of thrombosis during immobilisation is difficult to calculate because of the variety of definitions of immobilisation, it is well established as an independent risk factor for thrombosis.

Inherited risk factors for venous thromboembolism

Deficiencies of naturally occurring anti-coagulant proteins

The role of naturally occurring anti-coagulants in the prevention of VTE was discovered when the association between inherited deficiencies of anti-thrombin,[23] protein C, or protein S[33–35] and VTE was made between the 1960s and the 1980s. Homozygous deficiencies of protein C or protein S may cause extensive VTE manifestations, such as, neonatal purpura fulminans or warfarin-induced skin necrosis.[33–35] VTE may manifest at a young age (less than 40 to 45 years) in individuals with heterozygous deficiency of these anti-coagulants, often without environmental triggers and, sometimes, at unusual sites. These sites include cerebral sinuses, abdominal veins, and deep veins of the arms. Tendency to recurrent VTE and positive family history[34,35] is very common. Among the general population the prevalence of these conditions is low at less than 1%,[33–35] but

accounts for about 5 to 10% of patients with VTE.[33–35] The mode of inheritance is autosomal dominant. The reported prevalence of the defects varies significantly among different studies due to the selection criteria (lower in unselected patients and higher in patients referred to specialised centres for thrombophilia screening).[35] AT deficiency is the most thrombogenic of these conditions as shown in large family studies, while protein C or protein S deficiency[33] has significantly lower risk.

Factor V Leiden

Dahlbäck *et al.* in 1993 found that the plasma from members of a thrombophilic family failed to prolong the activated partial thromboplastin time after adding APC.[60] This condition was later called resistance to APC. This was subsequently attributed to the presence of a single amino acid substitution in one of the three cleavage sites of factor V by APC, an Arg instead of Gln at position 506, now best known as factor V Leiden.[60] This corresponds to a G to A substitution at nucleotide 1691 of the factor V gene. This is the most common cause of genetic thrombophilia, and its discovery has dramatically increased the understanding of the aetiology of VTE. The frequency of factor V Leiden is relatively high among Caucasians ranging between 2 and 15% in the general population[33–35] and up to 50% in selected patients with VTE.[33–35] Various studies have confirmed an increased risk of VTE for carriers.[61,62] The risk for a first episode of VTE as estimated in a large case control study is 7-fold and 80-fold for heterozygous and homozygous factor V Leiden carriers, respectively.[33–35] Carriers of factor V Leiden often have a mild thrombotic manifestation, such as, superficial vein thrombosis.[33–35] They rarely develop pulmonary embolism,[33–35] and may develop the first thrombotic symptoms at a relatively advanced age.[35]

Prothrombin G20210A mutation

This mutation was discovered in 1996, when candidate genes for thrombosis were investigated in patients with family clustering of VTE.[61] As for factor V Leiden and in contrast with the deficiencies of the naturally occurring anti-coagulants, this mutation causes a “gain

of function" in the coagulation system. Carriers of the mutation have about 30% higher plasma prothrombin levels than non-carriers,[61] associated with an increased potential for thrombin generation.[61] The mutation is present in 2 to 4% of the Caucasian population, and its prevalence in Southern Europe is twice higher than in Northern Europe.[34,35] This prevalence is the opposite of the geographical prevalence observed for factor V Leiden. In selected patients with VTE the prevalence of the mutation is up to 20%, and the relative risk in carriers is 2 to 4 times higher than in non-carriers.[34,35,62] Due to the relatively high frequency of the prothrombin mutation and the factor V Leiden in the general Caucasian population, their combined presence is not so rare. Not surprisingly, individuals who carry both mutations have a higher risk of developing a first[35] or recurrent[62] venous thrombotic episode than those with either mutation alone.

Other risk factors for venous thromboembolism

The following factors are of "mixed" inherited and acquired, and their role in determining VTE is usually less well-established.

Hyperhomocysteinaemia

Genetic defects cause an approximately 50% reduction in the activities of the corresponding enzymes, e.g., methylenetetrahydrofolate reductase (MTHFR). Acquired conditions include deficiencies of folate, cobalamine, and pyridoxine deficiencies, which are cofactors for homocysteine metabolism and chronic renal insufficiency. The association between moderate hyperhomocysteinaemia and VTE was made due to the high prevalence of this metabolic abnormality in a series of young patients with VTE in whom other causes of thrombophilia were excluded.[63] Since then several case-control studies have consistently demonstrated an increased thrombotic risk among individuals with hyperhomocysteinaemia. Other prospective studies, however, have found no association. Therefore, the causal relationship between hyperhomocysteinaemia and VTE is still unclear. There are also conflicting results on the role of the common homozygous mutation of MTHFR (cytosine to thymine at nucleotide 677), as a risk

factor for VTE. Although the homozygous variant is often associated with mild hyperhomocystaeinaemia (mainly in the presence of low folate concentration), many studies have failed to demonstrate a clear association.[64]

When associated with factor V Leiden, hyperhomocystaeinaemia or homozygosity for MTHFR increases the risk of VTE.[34,35] Therefore, the inclusion of this in the screening of thrombophilia is doubful. Hyperhomocystaeinaemia is corrected by vitamin supplementation, a treatment that is effective in the large majority of cases.

High levels of factor VIII

Elevated factor VIII is a risk factor for VTE.[65] A gradual dose-response relationship between risk of VTE and factor VIII levels has been observed.[34,35,65] The risk of thrombosis is independent of two major determinants of factor VIII levels, blood group and von Willebrand's factor levels.[65] The prevalence of high factor VIII levels among patients with thrombosis, taking as a cut-off value the 90th percentile of the distribution of values in a control population, varies from 19 to 25%.[65] Elevated factor VIII levels persist over time[65] and confer a high risk of recurrent VTE.[65] The latter finding may have important implications for the duration of treatment after the first episode of thrombosis.

High levels of factor IX, factor XI, and thrombin activatable fibrinolysis inhibitor (TAFI)

High plasma levels of factor IX or factor XI are associated with an increased risk of VTE.[34,35] The prevalence of patients with high levels of factor IX or factor XI was 20% and 19%, respectively, with an increased risk of VTE of 2-fold for both factors. A lower prevalence (14%) and increased thrombotic risk (odds ratio 1.7) has been found in association with high TAFI antigen.[35] As all of these findings derive from the same population-based case-control study of patients with a first episode of VTE (the Leiden Thrombophilia Study), further investigations are needed to confirm the causal relationship of these abnormalities with the occurrence of thrombosis.

Activated protein C resistance (without factor V Leiden)

Activated protein C (APC) resistance not caused by factor V Leiden may be of genetic or acquired origin. The former has been based on the description of families with APC resistance in the absence of factor V Leiden,[66] but other mutations are perhaps implicated, such as, the HR2 haplotype of factor V.[67] Among acquired causes of APC resistance the most common and well-established are pregnancy and the use of oral contraceptives.[67] A population-based study covering more than 15,000 individuals showed that the risk of thrombosis in the presence of APC resistance (in the absence of factor V Leiden) was nearly doubled.[67] In the Leiden Thrombophilia Study, a dose-response relationship between the degree of APC resistance and the risk of VTE was observed, with a 4-fold increased risk of VTE.[67] This study showed that the overall prevalence of APC resistance in patients with thrombosis was 36%, being 24% after the exclusion of factor V Leiden carriers. Therefore, the finding of APC resistance without factor V Leiden is to be expected in one in every 10 unselected patients with VTE, and the functional APC resistance assay should be a part of thrombophilia screening.

Risk stratification in venous thromboembolism

The high-risk (Table 4) category includes patients with the most severe forms of thrombophilia, including anti-thrombin deficiency, homozygous protein C or protein S deficiency, homozygous factor V Leiden, anti-phospholipid syndrome, combined thrombophilic defects, malignancy, and recurrent VTE. The low-risk category (Table 4) includes patients with only one episode of VTE that occurred in the presence of one or more transient risk factors, such as, surgery, immobilisation, pregnancy, oral contraceptive use, or hormone replacement therapy. Generally, patients in the high-risk category should be managed with indefinite anti-coagulant therapy (in case of malignancy, as long as the cancer is active), while short-term prophylaxis (up to 6 months) is an acceptable practice in patients belonging to the low-risk group. Patients who fall in other categories (Table 4), for example, those with mild thrombophilia (such as, heterozygous deficiencies of protein C or protein S, heterozygous factor

Table 4. Risk Stratification of Patients with Venous Thromboembolism

Risk Stratification	Patient Categories	Duration of Anti-coagulant Therapy
Low	Transient risk factors‡	Short-term, usually 3 months
Intermediate	Mild thrombophilia† Thrombosis in life-threatening sites (portal vein, mesenteric vein, cerebral vein), massive pulmonary embolism	Not well-established, but 6 to 24 months
High	Severe thrombophilia* Malignancy Recurrent VTE	Indefinite

*Includes AT deficiency, homozygous protein C, protein S, and F V Leiden, anti-phospholipid syndrome, and combined thrombophilic defects.
†Includes heterozygous protein C, protein S, F V Leiden, and P 20210A.
‡Includes immobilisation, surgery, pregnancy/puerperium, oral contraceptive use, and hormone replacement therapy.

V Leiden, or prothrombin mutations) and those with no obvious risk factors who had venous thrombosis in a life-endangering location (for example, portal vein, mesenteric veins, or cerebral veins) or had massive pulmonary embolism, can be grouped in an intermediate-risk category. For this group, there is no consensus about the duration of anti-coagulant therapy.

C) Haemostatic genetic risk factors in arterial thrombosis

Haemostasis plays an integral role in arterial thrombotic disease. Identifying risk factors has, however, proved to be surprisingly difficult.[68–75] Once established as a risk factor, a genetic polymorphism has the potential to aid selective prophylaxis and therapy of disease. Numerous reports have been published on polymorphisms of coagulation and fibrinolytic factors, of coagulation and fibrinolytic inhibitory proteins, and of platelet membrane glycoprotein receptors.[76–92] Although many studies have shown an association

between polymorphisms and disease, the collective outcome of these studies has primarily been inconsistent.

Heart disease, diabetes, and many cancers probably arise from the interaction of acquired and genetic factors. For arterial thrombotic diseases, such as, myocardial infarction and stroke a number of environmental risk factors are well-established, including smoking, diet, dyslipidaemia, hypertension, and impaired glucose metabolism. The role of haemostatic disorders in the development of arterial thrombosis is emerging.[68–75] Arterial thrombogenesis results from atherosclerosis and thrombosis, while atherosclerosis is a disease of the vessel wall resulting from chronic changes in vessel wall cellular components, occurring gradually over many years. The thrombotic event is an acute event thought to be triggered by tissue factor interaction with factor VIIa and almost certainly influenced by haemostatic factors, such as, fibrinogen, fibrinolytic factors, and platelet activation.[86–88] How the atherosclerotic process might be influenced by haemostatic factors is less clear.[72,77]

Some of the polymorphisms in coagulation and coagulation inhibitor genes studied include polymorphisms; of fibrinogen, factor VII, factor V/prothrombin, factor XIII, thrombomodulin/endothelial cell protein C receptor, fibrinolytic system genes (PAI-1), platelet glycoprotein receptors (GP IIb/IIIa, GP Ib-IX-V, GP Ia/Iia) and other coagulation proteins.[78–92]

Knowledge of genetic risk factors may define the pathogenesis of arterial disease and could ultimately help in the rational design of selective therapy. In approaching a large and often contradictory literature, it is helpful to have some basic premises in mind with which to assess the data. For this purpose, two critical premises should be considered. The first is fundamental; for a gene change to have an effect it must be mediated through a phenotype. In studies that report consistent relationships linking polymorphisms, phenotype, and clinical effect there can be some confidence that the genetic variation is influencing disease. In contrast, studies that report only the results of associations between polymorphisms and disease should be considered inadequate. This is because any statistically significant association between polymorphism and disease might well have arisen for reasons unrelated to the effect of its phenotype. Examples of such

confounding factors include play of chance, linkage with another gene locus, and poor study design resulting in bias. The second related premise to be used is whether a polymorphism is making an important contribution to disease and therefore, causing thrombosis.

Adopting the above strategy in analysing the data based on the relation between genotype, phenotype, and clinical outcome reveals that despite extensive investigation, there is still no clear reproducible evidence for the role of any haemostatic polymorphism in arterial thrombosis. This contrasts with the well-defined role of some of the same polymorphisms in VTE.[33,35] It is worth considering why this might be. There are fundamental differences between arterial and venous disease, with the dominant role of the vessel wall in the former. It can also be assumed that the haemostatic changes will play a crucial role in the thrombotic complications of arterial disease, mediated through atheromatous plaque rupture, fibrin generation, and platelet activation. It is, however, generally thought that arterial occlusion has a multifactorial aetiology, which conspires to undermine the integrity of the vessel wall and promote thrombosis. Some of these processes, which may involve haemostatic factors, will be influenced by genetic variation. Given the large number of factors, together with the lack of penetrance of disease in families, it is highly unlikely that individual haemostatic polymorphisms will have dominant influences on their own. Consequently, studies that focused only on the prevalence of a specific polymorphism in cohorts of patients (and controls), inevitably failed to show in a reproducible manner that the genetic variation is associated with disease. Apart from their lack of power, small studies are particularly prone to bias. The prevalence of polymorphisms in control groups may be underestimated, resulting in apparent, but spurious increased prevalences in case groups (stratification bias). Poor matching of cases and controls due to racial and population genetic heterogeneity is more likely with small numbers (admixture bias). It is certain that such factors have contributed to an over-representation of published studies reporting positive associations between polymorphisms and disease (publication bias).

A key consideration for future work must be the extent to which classical cardiovascular (acquired and genetically determined) risk factors for disease interact with polymorphisms of the haemostatic

system. Gene polymorphisms have existed within populations for thousands of years, while arterial disease has reached epidemic proportions only in the last century. This must have arisen through deleterious gene-environment interactions and suggests that the best means by which the influence of the genetic factor on disease will be reliably detected is by using studies that formally incorporate gene-environment interactions into their design. In retrospect, it is not surprising that so little progress has been made in this area. Fortunately, some studies had been designed at the outset to study interactions. These studies have produced plausible results of increasing risks of disease with increasing interaction, which fit current concepts of the aetiology of arterial disease. As clinical studies of interaction, however, require very large number of patients/controls, the power of most good studies has nevertheless been low. Consequently, there is an urgent need to address the role of haemostatic polymorphisms with well-designed studies that are larger by at least an order of magnitude. An upward scale change in terms of the number of potential risk alleles under evaluation may also be required, which is now possible with the microarray technologies. Such investigations may identify key combinations of polymorphisms that have low individual risks, but together may influence disease.

The prospect is for genetic screening of asymptomatic individuals, to identify their genetic risk profiles. On the basis of a screening programme, lifestyle advice and individualised pharmacological intervention programmes would be given to reduce future risks of disease. Today, it appears that insufficient progress has been made to justify the inclusion of haemostatic gene polymorphisms within such a population genetic screening programme.

SECTION III:

Thromoboprophylaxis for high-risk surgical patients

Major orthopaedic surgery

In the absence of prophylaxis, patients undergoing elective THR have a 2 to 5% incidence of symptomatic VTE and 0.1 to 2% fatal PE. Asymptomatic DVT, however, is found in 42 to 57%.[93,94] Primary

prophylaxis is the only effective method of reducing VTE in this population. Non-invasive screening techniques on discharge or venography are unacceptable alternatives.[105]

Non-pharmacological methods of prophylaxis

Physical methods of prophylaxis are designed to reduce stasis in the leg veins. Three types have been evaluated: graduated compression stockings (GCSS), intermittent pneumatic compression (IPC) devices, and venous foot pump (VFP). These methods are not associated with increased perioperative bleeding, but their problem is low compliance. Overall experience is also very limited in contrast with the pharmacological agents. These methods, unlike pharmacological agents, have not been shown to reduce mortality or PE and, therefore, appear to be less effective than pharmacological methods. In addition, GCSs are contraindicated in patients with peripheral vascular disease.

All three methods have been evaluated in patients undergoing THR, GCSs,[95] IPC,[96–101] and VFP.[102,103] There is no evidence that GCSs are effective. In two studies, IPC devices were as effective as warfarin.[97–99] In another study, IPC was less effective than warfarin in preventing proximal DVT.[100] In another randomised study, IPC of the calf and the thigh produced a 50% reduction in both distal and proximal DVT.[98] VFP is also effective.[102,103]

Pharmacological prophylaxis

Six different classes of anti-thrombotic agents have been evaluated in patients undergoing major orthopaedic surgery. These include low dose UFH, LMWH, aspirin, vitamin K antagonists, fondaparinux, and ximelagatran.

Aspirin was ineffective in reducing symptomatic VTE in the Pulmonary Embolism Prevention (PEP) Trial of 4088 patients undergoing THR or TKA.[104] Vitamin K antagonists and LMWH are effective and fairly common modalities in prophylaxis in this setting. LMWH is more effective than vitamin K antagonists and low dose UFH.[105–111] Recent evidence, however, suggests that fondaparinux is more effective than LMWH.[112]

Anderson *et al.* compared the relative efficacy of LMWH with that of UFH in six well-conducted trials for DVT prevention after THR.[106] LMWH was found to be significantly more effective than UFH in preventing DVT, as shown by venography, after total hip replacement. Meta-analysis has confirmed that the benefit of LMWH over UFH was only demonstrable for the prevention of proximal-vein thrombosis, while the rates of calf-vein thrombosis were similar in the two groups. The haemorrhagic risk was not significantly different between the two groups. Furthermore, the superiority of LMWH over oral anti-coagulants has emerged in almost all single trials dealing with this issue.[113–115]

In a recent, large, open-label trial THR patients were randomly assigned to in-hospital prophylaxis with either LMWH (enoxaparin, 30 mg × 2) or adjusted-dose warfarin.[113] Symptomatic, objectively documented VTE developed in a significantly lower proportion of patients treated with enoxaparin (0.3 vs. 1.1%). After three months of follow-up, however, this difference was no longer detectable (3.4 vs. 2.6%). In addition, major bleeding occurred more frequently in the enoxaparin treated group (1.2 vs. 0.6%).

Therefore, present experience consistently supports the view that LMWHs are more effective than UFH for the prevention of proximal DVT, with no additional haemorrhagic risk. They are more effective than oral anti-coagulants for the prevention of in-hospital (mostly distal) DVT, at the price of increased surgical site bleeding and wound haematoma. The choice between LMWH and warfarin should be tailored to the individual patient based on the clinical assessment of postoperative thrombosis and bleeding risk as well as the prophylaxis-specific cost and convenience.

There is still uncertainty about the ideal duration of prophylaxis, despite overwhelming evidence of the efficacy of anti-thrombotics in preventing postoperative VTE after orthopaedic surgery. Concern about the potential risk of pulmonary embolism from symptomless DVT, after hospital discharge, has led to the extension of the duration of prophylaxis for up to a month. Whether thromboprophylaxis should be extended after hospital discharge, however, is controversial.[116–121] Leclerc *et al.* studied 1984 consecutive patients who underwent hip or knee arthroplasty[121] and who received a mean

of 9 days enoxaparin prophylaxis (30 mg twice daily). The rates of VTE events during and after prophylaxis at 3 months follow-up were 2.1 and 2.1%, respectively. Following elective hip or knee replacement Heit *et al.* randomised 1195 patients to LMWH, to stop at the time of hospital discharge or continued for up to 6 weeks after surgery.[122] The rate of symptomatic, objectively confirmed VTE after a 3-month follow-up period was similarly low (2 and 1.5%, respectively) in the two groups.

To conclude, the optimal duration of prophylaxis after major orthopaedic surgery remains unclear.

Oncologic surgery

Extensive abdominal or pelvic surgery in cancer patients is associated with a remarkably high risk of developing postoperative VTE. Among pharmacological measures currently utilised for the prevention of postoperative DVT in cancer patients, LMWH have several selective advantage over UFH.[123–125]

D) Diagnosis of deep-vein thrombosis

Introduction

Many patients develop DVT in the presence of well-known risk factors, such as, immobility and malignancy. DVT can, however, occur unprovoked (idiopathic DVT). An underlying thrombophilia (inherited or acquired) may be present in some patients with idiopathic DVT, while the remainder have no demonstrable thrombophilia. The management of DVT is often straightforward. Problems leading to morbidity and mortality can result from misdiagnosis, treatment failure, and anti-coagulant-related haemorrhage.

Diagnosis of first episode of DVT

Symptoms of DVT vary and may be minimal or atypical. In addition, its diagnostic clinical features can be found in other disorders. DVT confirmed objectively is found in only about 25% of patients who present with such symptoms. As the clinical diagnosis is poor

and non-specific, confirmation with objective testing is paramount. In addition, although anti-coagulant therapy is highly effective, its unnecessary use should be avoided because it can cause serious morbidity and mortality. Despite the limitations of clinical diagnosis, the first step in evaluating a patient with suspected DVT remains history and full clinical examination.[126]

Clinical assessment

A proper clinical evaluation involves a careful assessment of the patient's symptoms, signs, and risk factors for venous thrombosis. Patients with symptomatic DVT can present with painful swelling, tenderness along the distribution of the deep leg veins, and localised erythema consequent to venous obstruction or perivascular inflammation. These signs can also be found in patients with cellulitis, ruptured Baker's cyst, superficial thrombophlebitis, and other musculoskeletal conditions. Therefore, the most important objective of the clinical evaluation is to determine whether the presenting features are more or less likely to be caused by one of these alternative diagnoses. If the patient has no known risk factors for venous thrombosis an alternative diagnosis is considered more likely and, therefore, the likelihood of DVT is significantly reduced. In contrast, if the patient has one or more known risk factors for thrombosis, the likelihood of DVT is increased. Well-established risk factors for venous thrombosis include recent major surgery or trauma, recent hospitalisation, malignancy, prolonged immobilisation, pregnancy and the puerperium, use of combined oral contraceptives or hormonal replacement therapy, and presence of anti-phospholipid syndrome and known heritable thrombophilia. Obesity, smoking, and long distance flights are considered weaker risk factors. Standardisation of the clinical assessment can be achieved by using one the clinical models available. The first model designed to assess the pretest probability (clinical likelihood) of DVT was developed and validated by Wells and colleagues (Table 5) in outpatients who presented with suspected DVT.[127,128] Following their clinical presentation, patients are stratified and assigned into low, medium, or high probability category for having DVT. Outpatients with classical findings of DVT and at least one risk factor have 85% probability of having DVT, while those with atypical features and

Table 5. Wells *et al.* Prior Clinical Probability (PCP) for Deep Vein Thrombosis

Clinical Features	Yes	No
Active cancer (on-going treatment or within previous 6 months or palliative)	1	0
Paralysis, paresis, or recent plaster immobilisation of the lower limbs	1	0
Recently bed-ridden for more than 3 days or major surgery, within 4 weeks	1	0
Localised tenderness along the distribution of the deep venous system	1	0
Entire leg swollen	1	0
Calf swelling by more than 3 cm when compared with the asymptotic leg (10 cm below the tibial tuberosity)	1	0
Pitting oedema (greater in the symptomatic leg)	1	0
Collateral superficial veins (non-varicose)	1	0
Intravenous drug abuse	1	0
Alternative diagnosis as likely or greater than that of DVT	−2	0

High score ≥ 3; moderate score 1–2; low score ≤ 0.

no identifiable risk factors have only about 5% probability of having thrombosis.[127] Shows a simplified version of the original model.[128] Although the identification of an alternative diagnosis may prove difficult, the model has been applied successfully to different patient settings, including patients in hospital and patients who present to the Accident and Emergency Department and acute admission and assessment wards.[129,130]

Wells has further streamlined the diagnostic process more recently by stratifying patients into two broad risk categories: "DVT unlikely" if the clinical score is 1 or less, and "DVT likely" if the score is more than 1.6.[131] Other investigators have adapted the modified model after removing the alternative diagnosis point. Junior medical staff were able to use this modified model without difficulty to triage patients with suspected DVT presenting to the emergency department.[132]

Initial objective testing

The most useful objective tests for diagnosing DVT are venous compression ultrasonography (CUS) and D-dimer testing. The need for

contrast venography (the reference standard for diagnosing DVT) has been markedly reduced by combining clinical assessment with compression ultrasonography and D-dimer testing. Validation studies have shown that diagnostic strategies incorporating clinical pretest probability, ultrasonography, and D-dimer testing are safe, reliable, and cost-effective in managing patients with suspected DVT.

Compression venous ultrasonograph

Compression venous ultrasonography (CUS) is the first objective test of choice in patients with high or moderate pretest probabilities. Lack of compressibility of the common femoral vein or popliteal vein or both is diagnostic for proximal DVT. Compression B-mode ultrasonography with or without colour duplex has sensitivity of 95% and specificity of up to 98% for diagnosing symptomatic, proximal DVT. It has sensitivity and specificity of 60 to 70% for isolated calf vein thrombosis.[133] Therefore, with concordant pretest probability and CUS of the proximal venous system, the accuracy and the predictive values of the positive and the negative combinations approach 100%.[134] Accordingly, DVT is confirmed when the pretest probability is intermediate or high and the CUS result is positive, while it is safe to exclude a diagnosis of DVT and withhold anti-coagulant therapy when the clinical suspicion is low and the CUS result is negative. In contrast, further objective testing will be required when other combinations occur because DVT is present in a range between 14 and 63%.[127,128] The major limitation of CUS is its reduced specificity and, therefore, accuracy in diagnosing distal calf thrombosis. Its limited availability outside routine working hours, including weekends and holidays, is also a problem.

D-dimer testing

D-dimer testing is used as the first objective test in patients with suspected DVT and low pretest probability. D-dimer assays were developed about 20 years ago to measure cross-linked fibrin degradation products. Since then many different assays have been evaluated for their accuracy and utility in diagnosing DVT (Table 6). In

Table 6. Performances of D-Dimer Testing in Suspected Venous Thromboembolism

Series	Patients n	Negative Predictive Value (NPV) % (95% CI)
Suspected DVT		
Classical ELISA	1337	96 (93–98)
Vidas-DD	785	98 (95–99)
Classical latex	733	92 (84–91)
Simplified	1108	92 (90–94)

general, a negative result using a sensitive D-dimer test is useful for excluding acute DVT. Conversely, a positive D-dimer result is not useful because the test lacks specificity. Furthermore, D-dimer levels are raised not only in acute thrombosis, but also in other conditions, such as, trauma, postoperative, immobility, pregnancy, infection, and malignancy. In addition, D-dimer levels are raised in elderly patients. Unfortunately, commercially available D-dimer assays vary in their sensitivity and specificity and, therefore, the performance of one assay cannot be extrapolated to another.[135] The most reliable and extensively evaluated tests are two rapid enzyme-linked immunosorbent assays (ELISAs; Instant-IA D-dimer, Stago, Asnie'res, France and VIDAS DD, bioMe'rieux, Marcy-l'Etoile, France) and a rapid whole blood assay (SimpliRED D-dimer, Agen Biomedical, Brisbane, Australia). The sensitivity of the rapid ELISAs is over 95% and that of the SimpliRED D-dimer assay is approximately 85%.

Earlier studies suggested that DVT can be safely excluded in outpatients who have a low pretest probability on standardised clinical assessment and a negative D-dimer result.[136,137] This proposed approach has now been validated by management studies that indicate an initial CUS is unnecessary in patients with a low pretest probability and a negative D-dimer result, because less than 2% of these patients will develop symptomatic DVT over the next 3 months.[132,138] Using this approach, an initial CUS can be avoided in 23 to 40% of patients who present with a suspected first episode of DVT.[132,138] Furthermore, management studies have also concluded that CUS can be combined with D-dimer testing to reduce serial CUS by about 60%.[139,140] Even independent of the pretest probability, if the initial

CUS result is negative and normal D-dimer result, further testing with serial CUS is unnecessary and anti-coagulant therapy can be withheld safely.[139–141] Therefore, D-dimer testing can greatly reduce the number of CUS required to investigate first episode of suspected DVT.

Follow-up testing

Serial CUS or venography is indicated in the presence of disagreement between the clinical assessment and CUS or D-dimer result. If the clinical probability is moderate or high, but the ultrasound is negative, further testing is indicated to detect a calf vein thrombus. Isolated calf vein thrombosis occurs in 15 to 20% of patients with symptomatic, confirmed thrombi and only about 20% of calf thrombi undetectable at initial presentation will extend proximally within 1 to 2 weeks of initial presentation.[142] Therefore, serial CUS (repeat CUS in 5 to 7 days or sooner, if clinically relevant) is a safe approach because it detects thrombus extension into the popliteal vein and because isolated calf vein thrombus that does not extend during the period of testing does not produce serious complications. Systematic review of management studies using serial CUS found a rate of conversion (from a negative to a positive) of only 1 to 2% during the period of testing, and the risk of a patient dying from pulmonary embolism while awaiting serial testing is 0.06% (95% CI, 0.00–0.32%).[134] Venography is indicated in patients unsuitable for serial CUS or those with severe symptoms and high clinical probability; those with poor cardiorespiratory reserve; and if the CUS result is inconclusive. It is also indicated in patients with unexplained swelling of the entire leg, but a negative CUS, as it is important to exclude an isolated iliac vein thrombus because the iliac veins are not routinely visualised with lower limb CUS. Isolated iliac vein thrombosis is infrequent, but it can occur in pregnancy and in patients who have extensive pelvic malignancy or have undergone recent pelvic surgery. An intraluminal filling defect on venography is considered as evidence of new or recent thrombosis. If the diagnosis is still inconclusive, it is reasonable to treat patients with anti-coagulant therapy and follow patients with abnormalities in distal veins with serial CUS.

Pregnant women with suspected DVT

The diagnosis of venous thrombosis in pregnancy can be challenging because: (1) unilateral left leg swelling can be caused by compression of the left iliac vein by the gravid uterus; (2) leg swelling can be caused by isolated common iliac vein thrombosis that may not be detectable by CUS, and (3) venographic examination of pelvic veins is problematic because of irradiation risk to the foetus. CUS is the initial test of choice in all patients, and the use of venography is limited to patients with suspected isolated iliac vein thrombosis, when the vein cannot be identified by CUS. Although venography exposes the foetus to irradiation, the risk of a fatal pulmonary embolism from a missed iliac thrombus probably outweighs the risk of radiation exposure to the foetus. Examination of the external and common iliac veins is technically feasible in the first two trimesters and can sometimes be done even in the third trimester with appropriate positioning. As in non-pregnant women, patients who have a negative initial ultrasound should be followed up with serial testing.

DVT diagnosis algorithm

This algorithm is based on the balance of evidence, a diagnostic strategy that combines clinical assessment using a standardised model, rapid ELISA D-dimer testing, and CUS. In patients with a low pretest probability, D-dimer testing should be the first investigation. If the D-dimer result is negative, further testing with CUS is unnecessary and DVT can be safely excluded; if the D-dimer result is positive, CUS should be performed. For all patients who have an intermediate or high pretest probability, the first investigation should be a CUS. If the ultrasound result is negative, D-dimer testing is helpful in selecting patients for further evaluation. Follow-up testing is not required if the D-dimer test is negative, while serial CUS or venography is indicated if the D-dimer result is positive (Fig. 14).

This strategy simplifies the diagnostic process and reduces the cost by reducing the number of patients who require both D-dimer testing and CUS examinations. As for all algorithms, there is room for the clinician to exercise their clinical judgment. For example, serial

CUS should be performed earlier than 5 to 7 days if the patient has severe or worsening symptoms, and venography should be considered in a patient with high clinical probability, normal CUS, and severe calf symptoms. Furthermore, if confirmatory tests cannot be performed in a timely manner and the clinical suspicion is high, empiric anti-coagulant therapy should be started before objective testing in the absence of contraindications.

Diagnosis of recurrent DVT

Although establishing a diagnosis of recurrent DVT is difficult because of the lack of a validated clinical model, and residual organised thrombus can complicate the interpretation of CUS, a similar strategy to that used in patients with suspected first episode of DVT is employed. This includes clinical assessment, CUS, and D-dimer testing in all patients who present with suspected recurrent DVT. Two important determinants influence pretest probability of recurrent DVT. These are a history of post-phlebitic syndrome (PPS) and the current use of anti-coagulant therapy. In patients with established PPS, it may be difficult to distinguish between an acute exacerbation of chronic symptoms and an episode of recurrent DVT. In patients already receiving anti-coagulant therapy, the likelihood of recurrence is reduced if the international normalised ratio (INR) is in the therapeutic range. Patients with advanced malignancy or anti-phospholipid syndrome are, however, at increased risk for recurrence despite a therapeutic INR value.[143,144] Although a new non-compressible segment on CUS is diagnostic of recurrent thrombosis, an earlier test result is needed to make this determination. CUS remains abnormal in up to 50% of patients one year after the initial diagnosis. Therefore, a single abnormal CUS, especially when there is no previous result available for comparison, does not necessarily confirm recurrent DVT.[144] In contrast, an intraluminal filling defect on venography is diagnostic for DVT, and a previous examination is not required for comparison. Venography is, however, technically demanding and invasive. It involves the risk of contrast related complications, is not readily available, and is impractical for repeated use. Although D-dimer testing has not been formally evaluated in

this setting, there is no reason why a negative D-dimer result should not be as reliable for excluding a diagnosis of recurrent DVT as it is for first episode of venous thrombosis. Based on the above considerations, a diagnosis of recurrent DVT is confirmed if there is a new non-compressible segment on CUS. Alternatively, recurrence is ruled out if the patient has a normal CUS and a negative D-dimer result. In patients who have a high clinical suspicion or other combinations of CUS and D-dimer results, venography or serial CUS is indicated.

Cost-effectiveness

The safety and cost-effectiveness of several strategies were compared in a recent decision analysis. For a mortality of untreated deep vein thrombosis of 2.5%, the difference in mortality was only 1 to 2 per 10,000 patients managed by the single ultrasound strategy compared to serial ultrasound.

Performing a single initial diagnostic ultrasound in association with an initial D-dimer reduced the requirement for ultrasound to 70 scans per 100 patients managed compared with 130 to 170 for the serial testing strategy (Table 7).[145] This enabled a cost reduction of 9 to 15% in the single scan compared with the serial ultrasound schemes. Therefore, in a patient with a suspected DVT, clinical probability with an initial ELISA D-dimer test followed by a single

Table 7. Cost-Effectiveness of Various Diagnostic Strategies for Deep Vein Thrombosis[145]

Strategy	*Lives Saved/1000 Patients	**Cost per QALY Saved ($)	Venography or Angiogram/100 Patients
Suspected DVT			
Serial CUS	4.3	15,475	na
+ D-dimer	4.3	14,934	na
PTP + serial CUS	4.4	14,339	19
PTP + D-dimer + single CUS	4.2	13,115	14

*Difference in mortality per 1000 patients compared with "no treatment" strategy in which no investigation or therapy is undertaken.

**Compared with no treatment strategy for a 60-year-old patient considered to have a life expectancy of 20.5 years.

diagnostic ultrasound with venography only in patients with a high clinical probability and a normal ultrasound appears to be safe and is a cost-effective strategy (Table 7).

E) Treatment of acute DVT

Two major advances in the treatment of DVT have been made in the last decade. First, is the introduction of low-molecular-weight heparin (LMWH) as a replacement for un-fractionated heparin (UFH) and, second, is the potential benefit from a longer duration of anti-coagulant therapy. Large meta-analyses have shown that unmonitored, weight-adjusted subcutaneous LMWH is as safe and as effective as UFH administered by continuous infusion guided by the activated partial thromboplastin time (aPTT).[146,147] As a result, subcutaneous LMWH is replacing intravenous UFH for the initial therapy of acute venous thromboembolism (VTE). Vitamin K antagonists are highly effective for long-term therapy, but they require laboratory monitoring and are problematic in some patients. Several new anti-coagulants with more convenient and potentially safer profiles are now undergoing clinical evaluation in randomised, controlled trials.

Initial anti-coagulant therapy

LMWH is the anti-coagulant of choice for initial therapy in the majority of patients with objectively confirmed DVT. The predictable pharmacokinetic properties enable LMWHs to be given as weight-adjusted subcutaneous injections without the need for laboratory monitoring.[148] Although laboratory monitoring is not usually required for patients receiving LMWHs, checking the 4-hour anti-Xa level is recommended in the following patient groups: advanced renal disease, pregnancy, children, and obese. If necessary, the LMWH dose should be adjusted.[148] In addition to their convenient dosing administration, LMWHs are more cost effective than UFH because the elimination of laboratory monitoring in most patients reduces the length of hospitalisation.[149] Another advantage of LMWHs over UFH is a lower risk of heparin-induced thrombocytopenia.[150] The majority of outpatients with newly diagnosed DVT are treated entirely at home.

This requires appropriate resources and infrastructure, including the ability to be able to teach all suitable patients or family members to administer subcutaneous injections, or arrange for the home support of a district nurse in those who are visually impaired or physically unable to inject themselves. Outpatient treatment requires an organised service with dedicated staff to provide patient support and education. Despite the disadvantages of UFH, it is often used in patients with extensive iliofemoral DVT with circulatory compromise and those who are haemodynamically unstable from associated major pulmonary embolism, because these groups were excluded in clinical trials that compared LMWHs with UFH. The usual intravenous regimen for UFH is a loading dose of 5000 U followed by a continuous infusion of around 1400 U hourly. The dose of UFH is adjusted according to the aPTT by following a validated standard nomogram to maintain a therapeutic heparin level.[148] Alternatively, a weight adjusted loading dose and nomogram can be used.[151] If subcutaneous UFH is used, it is given at a starting dose of 17,500 U twice daily, and the dose is adjusted to achieve a therapeutic aPTT at six hours after the initial injection.[148] In patients requiring large doses of UFH ($\geq$ 35,000 U/24 h), the heparin level should be monitored by anti-Xa assay. LMWH or UFH should be administered for a minimum of 5 days in patients with uncomplicated thrombosis and for 7 days or longer in patients who have extensive disease (e.g., iliofemoral DVT or massive pulmonary embolism). Oral anti-coagulant therapy can be started on the first day of treatment, and LMWH/UFH should not be stopped until the INR has been at least 2.0 for 2 consecutive days. A baseline platelet count and on days 5 to 7 should be done to check for heparin-induced thrombocytopenia if the patient is receiving UFH.

Long-term anti-coagulant therapy

After an initial course of LMWH or UFH, continuing anti-coagulant therapy with oral vitamin-K antagonists is required to prevent recurrence. Warfarin is the most common agent used in UK. The use of a loading dose is discouraged because it may be associated

with a transient period of excessive anti-coagulation, without a corresponding anti-thrombotic effect.[152] The INR is measured after the first 2 or 3 doses of warfarin, and subsequent doses are adjusted to maintain the INR within the target range. As the therapeutic window for oral anti-coagulant therapy is narrow, frequent monitoring of the INR is essential to reduce the risks of recurrent thrombosis and anti-coagulant-related haemorrhage (ARH). Appropriate adjustments in the dose of warfarin usually require twice-weekly monitoring for the first 1 to 2 weeks, followed by weekly monitoring for the next 4 weeks, then once every 2 weeks for a month and, finally, every 4 weeks if the INRs have remained in the therapeutic range on a stable warfarin dose and the patient has not experienced any adverse effects. It is wise to monitor the INR at 4-week interval even in patients who have maintained a stable warfarin dose because of the potential interactions of warfarin with food or drugs. If there are changes in the patient's medications, more frequent monitoring is needed until a stable dose response is achieved.[153] Because oral anti-coagulant therapy is inconvenient, LMWH is being evaluated as an alternative for long-term treatment of VTE. LMWH has a number of advantages over warfarin. First, because LMWH does not require INR monitoring, it can be used when laboratory monitoring is problematic (e.g., difficult venous access). Second, LMWH has a more rapid onset and offset of action than warfarin. Therefore, it is more convenient to use in patients who require dental or surgical procedures while anti-coagulated. Third, there is a clinical impression that LMWH is more effective than warfarin in patients with thrombosis and cancer and in those who develop recurrent thrombosis despite therapeutic warfarin therapy. Despite these advantages, however, the routine use of LMWH is not practical or economical because LMWH requires administration by subcutaneous injection and is more expensive than warfarin. LMWHs may be difficult to reverse completely in the event of life-threatening haemorrhage. Randomised controlled trials comparing LMWH with oral anti-coagulant therapy have shown that the rates of recurrent thrombosis and major bleeding between the two treatment groups are similar.[154,155]

Duration of anti-coagulant therapy

The duration of anti-coagulant therapy is influenced by balancing the risks of recurrence of thrombosis and of anti-coagulant related haemorrhage (ARH), and by the patient preference. The risk of bleeding during the initial period of anti-coagulation with UFH or LMWHs is 2 to 5%, while the estimated risk of major bleeding with oral anti-coagulant therapy is about 3% annually.[156] As 20% of major bleeds are fatal, the annual case fatality rate from ARH is about 0.6%. The risk of bleeding is increased by patient-specific factors, such as, age (65 years or older) and co-morbidity (renal failure, liver disease, diabetes, peptic ulcer disease, cerebrovascular disease, malignancy) and by the concomitant use of anti-platelet agents.[157,158] Evidence also indicates that the risk of bleeding on anti-coagulant therapy is reduced over time, so the long-term fatality rate is likely to be lower in patients who have tolerated months or years of anti-coagulant treatment without bleeding. On the other hand, the case fatality rate from recurrent VTE is about 5%, with the rate being higher within the first 3 months of an episode of pulmonary embolism. Therefore, at an annual recurrence rate of 12%, the risk of death from recurrent thrombosis is balanced by the risk of death from ARH. In general, patients should be treated with anti-coagulant therapy for a minimum of 3 months. Patients with a reversible risk factor have a low risk of recurrence after 3 months of anti-coagulant therapy. In contrast, patients with idiopathic or unprovoked DVT who are treated for only 3 months have 10 to 27% risk of recurrence in the year after anti-coagulants are discontinued.[159–161] Recent evidence suggests that extending therapy beyond 6 months in patients with idiopathic thrombosis does not reduce the risk of recurrent thrombosis to less than 10% in the year after discontinuing anti-coagulant therapy. Continuing warfarin after this period protects the patient against future recurrence, but also exposes the patient to the risk of ARH. Based on the results of prospective studies and extrapolation from studies on the risk of recurrence after a first episode of venous thrombosis, patients can be stratified into low, moderate, high, and very high-risk groups for recurrence when anti-coagulants are discontinued. Low-risk patients are those who had an important risk factor for thrombosis (e.g., major surgery, pelvic or leg

trauma, or major medical illness) from which they have fully recovered. Their risk of recurrence when anti-coagulants are discontinued at 3 months is estimated to be less than 5% in the next year and somewhat lesser in subsequent years. These patients should be encouraged to have prophylactic anti-coagulants if exposed to a high-risk state and, in general, should be encouraged to seek alternatives to oestrogens for contraception or post-menopausal use. Moderate-risk patients are those without inherited or acquired thrombophilia who had a thromboembolic event in association with a minor risk factor, such as, oestrogen use or long distance travel. Their risk of recurrent thrombosis after 6 months of anti-coagulants is likely to be less than 10% in the year after stopping anti-coagulants, provided that the precipitating risk factor is avoided; they should be treated with anti-coagulants for 6 months. If, however, the precipitating factor cannot be avoided (e.g., oestrogens) they should be given the option of remaining on anti-coagulants during the period of exposure. High-risk patients are those who have an unprovoked venous thromboembolic event and who either have no demonstrable thrombophilia or are heterozygous for factor V Leiden or the prothrombin G20210A mutation. Their risk of recurrence after 6 months of anti-coagulant therapy is likely to be about 10% per annum. In general, anti-coagulant therapy can be stopped after 6 months in these high-risk patients. If, however, the bleeding risk is low, the INR monitoring is smooth and convenient, and the patient prefers to remain on anti-coagulant therapy, treatment can be continued and the treatment duration reviewed on an annual basis. Very high-risk patients are those with more than one unprovoked thromboembolic event; patients with inherited deficiencies of anti-thrombin, protein C, or protein S; those with anti-phospholipid antibody syndrome or advanced malignancy; and those who are homozygous for factor V Leiden or prothrombin gene mutation or double heterozygotes. The risk of recurrence after a 6-month course of anti-coagulants is likely to be more than 12% annually and, in general, these patients should remain on anti-coagulants indefinitely. Firm evidence for this last recommendation is not available, but because the listed thrombophilic states are strong risk factors for a first episode of VTE, they are also likely to increase the risk of recurrent VTE.

PPS and its prevention

Following an episode of DVT, one-fifth of patients may experience PPS.[162] Leg pain and swelling exacerbated by standing and physical activity and reduced with elevation of the affected leg are typical features. In severe cases, venous ulceration can develop. PPS occurs as a result of venous hypertension, most commonly caused by venous valvular incompetence and less frequently by persistent venous obstruction. Not all patients with valvular incompetence develop the clinical features of PPS.[163] Two approaches have been proposed to prevent and treat PPS, thrombolytic therapy to reduce the damage to venous valves and graduated compression stockings to counter venous hypertension. Results from clinical trials have, however, not clearly shown beneficial effects with either method.[162,164,165] The development of PPS is more likely after recurrent episodes of DVT. Therefore, every effort should be made to reduce the likelihood of recurrent thrombosis by using an appropriate course of anti-coagulant therapy for the initial episode and anti-coagulant prophylaxis in subsequent high-risk situations.

Treatment of DVT in pregnancy

UFH was the standard treatment for DVT in pregnant women prior to the introduction of LMWHs. Warfarin is generally avoided because of the risk of warfarin embryopathy and other potential teratogenic effects. UFH has a number of limitations, including heparin-induced osteoporosis, the need for twice-daily subcutaneous injections, and the necessity for aPTT monitoring. These disadvantages are virtually eliminated with LMWH. Although there have been no randomised controlled trials comparing UFH with LMWH in pregnancy, there is no reason to expect that the advantages of LMWH in the non-pregnant population would not apply to pregnant women.[166] In addition to the convenience of once-daily injection without the need for frequent laboratory monitoring, like UFH, LMWH does not cross the placenta. Therefore, it is not teratogenic and is not excreted into breast milk. Pregnant women are treated throughout their pregnancy with LMWH and arrange for a planned induction of labour

in consultation with the obstetrician. The controlled delivery date enables discontinuation of LMWH 24 hours prior to induction, reducing the risk of bleeding during delivery.

Screening for thrombophilia

The indications for screening patients, who present with a first episode of venous thrombosis to identify underlying thrombophilia, are controversial. From a practical viewpoint, screening would be indicated if the results influenced the duration of anti-coagulant therapy or the need for family counseling. The duration of anti-coagulant therapy is influenced by finding deficiencies in anti-thrombin, protein C, or protein S, homozygous factor V Leiden, homozygous prothrombin gene mutation double heterozygosity, and persistently elevated anti-phospholipid antibodies. Family counselling is particularly important for female carriers who are contemplating oestrogen use. Based on these considerations, we think that it is reasonable to perform screening for thrombophilia in the following groups: first episode of idiopathic thrombosis at age 50 or younger; history of two or more episodes of recurrent thrombosis, especially if the events were unprovoked; thrombosis in an unusual site (e.g., cerebral, mesenteric, retinal); positive family history with two or more first-degree relatives with documented venous thrombosis; women who develop pregnancy associated thrombosis or in the setting of a hormonal agent; and women who have unexplained recurrent pregnancy loss. This latter group requires special consideration because anti-coagulant and anti-platelet therapy may improve future pregnancy outcomes if underlying thrombophilia is documented.[167] A standard screening panel includes functional assays for anti-thrombin and protein C, free protein S level, activated protein C resistance assay with DNA testing for factor V Leiden, molecular assay for prothrombin G20210A mutation, a phospholipid-based clotting test for lupus anti-coagulant, ELISAs for anti-cardiolipin antibodies, and a fasting homocysteine level.[168]

New anti-thrombotic agents

Several new anti-thrombotic agents that target selectively single molecules in the coagulation cascade are under development. Parenteral

direct inhibitors of thrombin; hirudin and argatroban have been approved for the treatment of HIT. Danaparoid, a heparnoid can be also used for HIT. The synthetic pentasaccharide, fondaparinux (Arixtra) and the oral direct thrombin inhibitor ximelagatran (Melagatran) are two potential additional agents.

Synthetic pentasaccharide is administered as a once-daily subcutaneous injection and is being compared with UFH for initial treatment of DVT and pulmonary embolism. This new agent has the advantage of a longer half-life than LMWH and is unlikely to produce heparin-induced thrombocytopenia. A newer form of synthetic pentasaccharide with a longer half-life that enables once-weekly subcutaneous injection is also being evaluated for the out-of-hospital longer-term treatment of patients with VTE. Large randomized controlled trials have shown that pentasaccharide is superior to enoxaparin in thromboprophylaxis after major orthopaedic surgery.[167,170] Ximelagatran is administered orally and is being compared against standard anticoagulants for thromboprophylaxis in orthopaedic surgery, atrial fibrillation, as well as initial and long-term treatment of VTE.[171,172]

Thrombolytic therapy for DVT

The role of thrombolysis in DVT treatment remains ill-defined. Venographic studies, thrombolytic agents can produce rapid lysis of venous thromboemboli and restore venous flow. Consequently, thrombolytic therapy has the potential to provide prompt symptomatic relief and reduce the risk of the PPS.[173,174] Despite documented improvements on radiologic imaging, however, appropriate studies have not been performed to demonstrate improvements over standard anticoagulant therapy alone, using clinically relevant outcomes. Thrombolytic therapy increases the risk of major bleeding about 3-fold over that observed with UFH alone, and the observed rate of intracranial haemorrhage is approximately 2%.[175] There is no agreement on whether systemic or catheter-directed thrombolysis is the preferred method of delivery. A recent randomised, controlled trial comparing UFH alone with four regimens of systemic or regional thrombolysis showed greater venographic improvement at 12 months with systemic thrombolytic therapy, but at a cost of substantially higher rates of major bleeding and pulmonary embolism compared with

UFH.[176] Therefore, even if thrombolysis is effective in reducing the risk of recurrent thrombosis or PPS, the cost, the bleeding risk, and the technical expertise required for this aggressive therapy are major obstacles to its routine use. Most clinicians limit thrombolytic therapy to younger patients with massive iliofemoral vein thrombosis, who have limb-threatening circulatory compromise.

Vena caval interruption

In the presence of a contraindication to anti-coagulant therapy, an inferior vena caval filter is placed in patients with iliofemoral DVT. These circumstances include active bleeding, risk of serious bleeding, and failure of therapeutic anti-coagulant therapy. The use of filters remains controversial in other clinical situations, for example, for preventing embolisation of "free-floating" thrombi in iliofemoral territory and as the first-line treatment (alone) in patients with central nervous system malignancy and acute DVT.[177] Only one randomised, controlled trial has evaluated the use of vena caval filters in patients with proximal DVT, all of whom also received anti-coagulant therapy.[178] There was a significant initial reduction in the incidence of pulmonary embolism in the filter group, but this advantage was lost with longer follow-up. In addition, patients with a filter had a higher risk of recurrent DVT and there was no difference in the overall mortality at 2 years following the study. Similar results are reported by a population-based analysis in more than 3600 patients in whom a filter was inserted for DVT.[179] Other potential situations where caval interruption may be indicated include: patients with a newly diagnosed proximal DVT or pulmonary embolism who have to undergo urgent surgery; who have severe thrombocytopenia; or have active and potentially life-threatening bleeding. In all cases, anti-coagulant therapy is restarted when normal haemostasis is achieved.

SECURING HAEMOSTASIS IN HAEMOSTATIC FAILURE

General aspects of anti-coagulant therapy

This is achieved by anti-coagulation initially by heparin and subsequently by warfarin for 3 to 6 months. Anti-coagulants are commonly

used in cardiological practice and in the prevention and the treatment of deep venous thrombosis (DVT) and pulmonary thrombosis (PE). The objective of anti-coagulant treatment is to achieve a level of anti-coagulant at which there is complete anti-thrombotic effect, but no increased risk of bleeding. This ideal is not achieved with current drugs, the main ones in the UK being heparin and warfarin. Careful and regular laboratory control is required to achieve a compromise between efficacy and risk.

Heparin

Unfractionated heparin (UFH) is a naturally occurring strongly anionic mucopolysaccharide, MW 5000–35,000 d. Its main action is to augment the effect of the physiological anti-coagulant, anti-thrombin (AT). Arginine residues on the AT molecule interact with serine residues on certain activated coagulation factors — thrombin, Xa, IXa, XIa, XIIa-forming irreversible complexes, which are removed by reticulo-endothelial cells. Heparin increases the inhibitory action of AT by 1000-fold. Low molecular weight heparin (LMWH) MW 2000–8000 d are prepared from UFH by chemical or enzymatic depolymerisation. Acceleration of inhibition of factor Xa requires only the pentasaccharide sequence, but acceleration of thrombin inhibition requires a minimum total chain length of 18 saccharides (MW 5000 d). Therefore, in all LMWHs the anti-Xa activity is greater than the anti-IIa activity.[146–149]

The usual routes of administration are by continuous IVI for UFH (half-life about 1 hour); twice daily SC injections have also been used. LMWH is usually given by once or twice daliy SC injection.

Laboratory monitoring

The APTT should be measured 4 to 6 hours after starting the IV UFH and, thereafter, once daily aiming to keep the APTT ratio between 1.5–2.5. The platelet count should also be monitored because of the risk (1–2%), of heparin-induced thrombocytopenia (HIT), which may be associated with arterial thrombosis.

No laboratory monitoring is required for LMWH therapy in routine circumstances. For certain patient groups this will be required

and is carried out by measuring anti-Xa levels (see diagnosis and treatment of DVT).

Side effects

Bleeding is the most common side effect.[157] The infusion should be stopped, a clotting screen checked, and blood transfusion may be necessary. Due to its short half-life, heparin may be recommenced after few hours at a lower dose. If bleeding is severe, heparin can be neutralised by IV administration of protamine sulphate. Other side effects include HIT,[180] osteopenia (on prolonged administration), skin necrosis, alopecia, and hypersensitivity reactions.[180]

Warfarin

It antagonises vitamin K, required for gamma carboxylation of certain glutamic acid residues that facilitate calcium binding of coagulation factors II, VII, IX, and X and the naturally occurring anti-coagulants proteins C and S. Warfarin takes 3 to 5 days to achieve an anti-coagulant effect which is dependent on achieving a sufficiently low level of factor II (half-life 60 hours). Therefore, heparin and warfarin should be overlapped for at least 72 hours, and heparin should not be stopped until the International Normalised Ratio (INR) is > 2.0 (usually after 5 days of overlap). A number of drugs may interact with warfarin (potentiate or antagonise) and change warfarin requirements, sometimes dramatically.[153,181,182]

Laboratory monitoring

The INR is a standardised PT. The usual recommended therapeutic range is 2 to 3 or 3 to 4.5 depending upon the indication. The dose of heparin may need to be reduced as the INR rises. The patient should be counselled about warfarin treatment and seen in the anti-coagulant clinic within a week of discharge.

Side effects

Bleeding, usually related to overdosage, is the most common side effect. If the INR is > 4.5 and there is no bleeding, stop the warfarin,

check the INR at 24 to 48 hours, and restart warfarin at a lower dosage. Serious bleeding necessitates treatment with fresh frozen plasma or clotting factor II, IX, X, and VII concentrates. Vitamin K1 given IV slowly acts within a few hours, but may cause problems with reanti-coagulation for unpredictable lengths of time (up to 3 weeks). Small doses are advised (1 to 2 mg) unless further warfarinisation is not required (10 mg). Other side effects include skin necrosis (protein C or S deficiencies), skin rashes, or alopecia.[156,157,182]

Pregnancy

Warfarin crosses the placenta and is teratogenic, particularly between weeks 6 to 12. Later in pregnancy it may precipitate intracerebral haemorrhage in the fetus. Heparin does not cross the placenta and is the anti-coagulant of choice during pregnancy. Neither heparin nor warfarin is excreted in breast milk.

Advantages of LMWH (Table 8)

1. LMWH have a greater bioavailability at low doses, longer half-life, and more predictable response when administered at fixed doses than UFH.
2. No need for routine laboratory monitoring.

Table 8. Comparison of the Properties of LMWH and UFH

Property	UFH	LMWH
Mean MW (range)	15 (4–30)	4.5 (2.4–15)
Saccaride units (mean)	40–50	13–22
Anti-Xa: Anti-IIa	1:1	2:1–4:1
Inhibited by PF4	Yes	No
Anti-thrombotic effect via anti-IIa	Yes	Yes
Inhibits platelet function	Yes	No
Bioavailability (at low dose)	40%	100%
Elimination	Hepatic and renal	Renal
Half-life of anti-Xa: IV	1 hour	2 hour
SC	2 hour	4 hour
Monitoring required	Yes	No
Frequency of HIT	High	Very low

3. LMWH provide an anti-thrombotic efficacy in the prevention of postoperative DVT and PE, at least as good as UFH in general surgery. This effect may be obtained by once daily SC dose.
4. In orthopaedic surgery, LMWH is superior to UFH as prophylaxis for postoperative DVT, in terms of efficacy without increasing the bleeding risk.
5. SC LMWH is as effective and safe as UFH (IV or SC) for the initial treatment of DVT.
6. LMWH is effective as anti-coagulant in chronic haemodialysis, given as a single bolus injection.
7. LMWH treatment may be associated with a lower incidence of thrombocytopenia and fewer cases of heparin-induced thrombocytopenia and thrombosis.
8. LMWH can be used to treat some patients with DVT and PE as outpatients and at home.
9. LMWH is associated with less osteopenia and heparin-induced osteoporosis related clinical fractures.

Disadvantages of LMWH; cost

Heparin-induced thrombocytopenia

The incidence of heparin-induced thrombocytopenia (HIT) with full dose unfractionated heparin appears to be around 1 to 3%, higher with heparin of bovine than porcine origin, and the incidence is somewhat less with heparin used at prophylactic doses and new LMWHs. HIT has been divided into two groups. Type I is a mild immediate transient thrombocytopenia that occurs soon after heparin exposure. It is seldom associated with a platelet count below 100×10^9/l and resolves spontaneously even if treatment is continued. This very seldom, if ever, results in clinical problems. Type II has its onset after greater than 5 days' exposure to heparin. It is associated with a platelet count often below 100×10^9/l and is the immune mediated form that is associated with arterial and venous occlusion.[180]

Diagnosis remains primarily clinical being based on a fall in the platelet count to less than half the baseline value and usually lower than 100×10^9/l with, onset 5 or more days after exposure to

heparin.[180] Other causes of thrombocytopenia, such as, sepsis and ITP should be excluded and the thrombocytopenia will resolve following heparin withdrawal, usually after 5 to 7 days, but this can take up to a month. Clinical diagnosis can be supplemented by positive laboratory tests for the presence of a heparin-dependent antibody.

HIT may be preventable by minimising the duration of heparin exposure and performing regular platelet counts on patients with heparin and ensuring prompt withdrawal of therapy should the platelet count fall.

The treatment of HIT involves the immediate cessation of exposure to heparin. In the majority of cases, particularly where thrombosis has occurred, it will be necessary to commence warfarin. There is often a need for a short acting anti-coagulant to substitute for heparin until warfarin has reached therapeutic levels. Therapy is between the heparanoid Danaparoid, which has only 10% cross-reactivity with unfractionated heparin or hirudin which does not cross-react in HIT. LMWH suffers 40 to 90% incidence of cross-reactivity with unfractionated heparin. Other treatments, such as, ancrod is not used routinely.[180] Fondaparinux is another potential alternative in HIT.[112]

As the platelet count seldom falls into single figures, the placement of IVC filters and the use of fibrinolytics and surgery have all been safely performed to alleviate thrombotic complications despite the thrombocytopenia.

The mechanism of HIT is due to the formation of antibodies against the complex of heparin with platelet factor-4, a highly positively charged heparin binding protein released from platelet α-granules. The immune complex with heparin and PF-4 binds to platelet surface FC receptors, and this binding results in *in vivo* platelet activation and subsequent aggregation. The mechanisms of thrombosis are probably multifactorial as in addition to *in vivo* platelet aggregation, there is also evidence of activation of the coagulation cascade with increased levels of markers of thrombin generation and depletion of the proteins of the natural anti-coagulant pathway. Furthermore, endothelial cell immune mediated damage results in the exposure of endothelial cell tissue factor and the formation of a procoagulant endothelial surface to favour thrombosis.[180]

Table 9. INR Targets for Anti-coagulation

INR (International Randomised Ratio)	Clinical State
2.0–2.5	Prophylaxis of DVT, including high risk surgery
2.0–3.0	Hip surgery, repair of fractures of femur Treatment of DVT and pulmonary embolism Prevention of VTE after myocardial infarction Mitral stenosis with embolism Atrial fibrillation Transient ischaemic attacks
3.0–4.5	Recurrent DVT Recurrent pulmonary embolism Arterial disease including myocardial infarction and grafts Prosthetic valves and grafts

Accepted target INR therapeutic ranges

The current accepted INR targets for anti-coagulation as recommended by the British Committee for Standardisation in Haematology[182] are summarised in Table 9.

Potential factors that interfere with anti-coagulant control

Clinical conditions with potentiating effect on anti-coagulation

Alcohol excess
Cardiac failure
Cholestasis
Diarrhoea (enteritis)
Fever
Gastrocolic fistula
Hypoalbuminaemia
Liver damage (*decreased synthesis of vitamin K factors*)
Malnutrition
Severe weight reduction regimens
Renal impairment
Thyrotoxicosis

Pharmacological agents (Table 10)

Table 10. Drugs that Interfere with the Control of Anti-coagulant Therapy[182]

Potentiation of oral anti-coagulants Drugs that increase the effect of coumarins	**Inhibition of oral anti-coagulants** Drugs that reduce the action of coumarins
Reduced binding to serum albumin	*Acceleration of hepatic microsomal degradation*
Phenylbutazone	
Sulphonamides	Barbiturates
Co-trimoxazole	Rifampicin
Amidarone	
Inhibition of hepatic microsomal degradation	*Enhanced synthesis of clotting factors*
Cimetidine	Oral contraceptives
Allopurinol	
Tricyclic anti-depressants	
Metronidazole	
Sulphonamides	
Alteration of hepatic receptor for drug	
Thyroxine	
Glucagon	
Quinidine	
Decreased absorption of vitamin K	
Laxatives	

NB: Patients are also more likely to bleed if taking anti-platelet agents (e.g., NSAIDs, dipyridamole, or aspirin).

Conditions with inhibitory effect on anti-coagulation

Pregnancy
Hereditary resistance to warfarin

Managing anti-coagulation in patients undergoing surgery

In patients who are already anti-coagulated and contemplating surgery, it is important to balance the risk of haemorrhage if the INR is not reduced against the risk of thromboembolism if it is reduced too low for too long. The patient should be referred to the anti-coagulant clinic well in advance of any planned surgery to advise patients about their anti-coagulant therapy modification.

Minor surgery. For most minor procedures, e.g., dental work, it is sufficient to simply omit warfarin for 2 days prior to the procedure and restart with the usual maintenance dose immediately afterwards (the same day). Alternatively, warfarin could be stopped for 3 days before the procedure and recommenced the day immediately before the procedure (it takes time for warfarin effect to be established). If any problems are anticipated or there have been problems in the past, then the INR should be checked beforehand. If INR < 2.5 then it is safe to proceed (Fig. 12).[183]

Extreme caution should be exercised with patients who have prosthetic heart valves. The INR should not be allowed to drop too low. If several extractions are required or there is any doubt, then follow the guidelines for major procedures.

Intermediate and major surgery (Fig. 13)

(I) *Low risk patients*

E.g., Mitral valve disease, atrial fibrillation, cardiomyopathy[183]

Stop warfarin 3 days prior to surgery.
Start heparin 5000 iu s/c 3 times daily or equivalent LMWH dose when INR < 2.5.
Avoid giving heparin < 2 hours before surgery.
Chech INR < 2 and APTT < 45 seconds before surgery.
Restart warfarin postoperatively and overlap with heparin until INR > 2.5 for at least 2 consecutive days.

(II) *High risk patients*

E.g., Mechanical valve replacement, recurrent or acute thromboembolism, known thrombophilia[183]

The management of these patients requires considerable effort and attention. Coordination and communication between the surgeons and the anti-coagulant clinic team is paramount.
Stop warfarin > 3 days before surgery.
When INR < 2.5 start iv heparin at 20,000 iu per 24 hours and adjust to give APTT 1.5–2.5 times control if patient is hospitalised.
Alternatively give LMWH therapeutic dose as an outpatient.

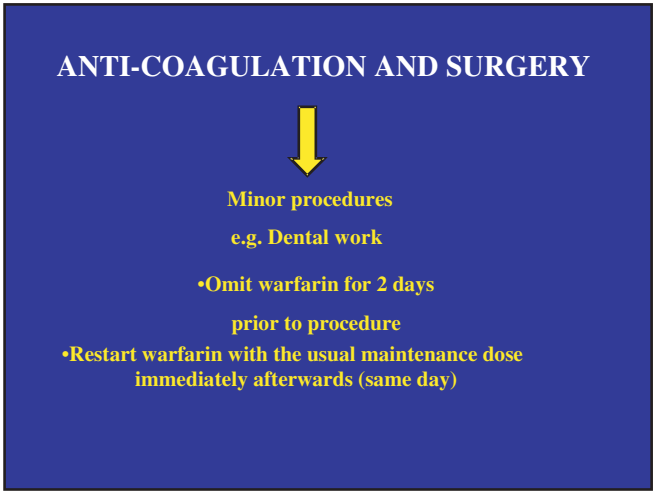


Fig. 12 Flow chart summarising the management of oral anti-coagulation in minor surgical procedures.

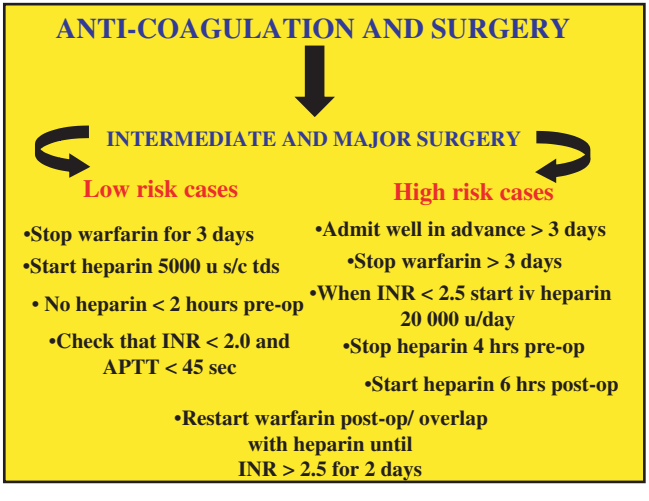


Fig. 13 Flow chart summarising the management of oral anti-coagulation in intermediate and major surgical procedures.

Stop heparin 4 hours (if LMWH, stop it 12–24 hours prior to surgery depending on dose and type of LMWH) prior to surgery and check that INR < 2.0 and APTT < 45 seconds immediately before the procedure. If not, then it will probably be sufficient to wait for 1 to 2 hours and repeat the tests.

Restart heparin 6 hours postoperatively and re-establish therapeutic levels.
When stable restart warfarin and overlap with heparin for at least 2 days.
Do not give a loading dose and remember that the patient is not eating and vitamin K deficiency may be a problem.
Stop heparin when INR > 2.5. If re-operation is possible, continue with heparin.

Reducing the risk of thromboembolism

The risk of thromboembolism and associated morbidity depends on the indication for anti-coagulation: if and how long before patients have had previous episodes of thromboembolism and whether or not surgery increases the risk of thromboembolism. The risk of preoperative bleeding is generally low, but is high following major surgery. As the risk of thromboembolism and bleeding are often influenced by the surgical procedure, anti-coagulant management needs to be considered separately for the pre- and postoperative periods.

Preoperative

Indications for warfarin

To assess the risks associated with temporarily stopping anti-coagulants, the consequences, as well as the absolute risk, of a thromboembolic event need to be considered. Arterial thromboembolism (ATE) often results in death (~40%) or major disability (~20%) whereas venous thromboembolism (VTE) rarely presents as sudden death (~5 to 10%), and major disability is also unusual (<5%) in patients with treated VTE.[183]

(a) Arterial indications for anti-coagulation

Primary prophylaxis of ATE is most commonly undertaken in patients with atrial fibrillation (AF), valvular heart disease, and recent myocardial infarct. Secondary prophylaxis is undertaken after patients (with or without the above conditions), have had an ATE event (usually stroke). Previous thromboembolism is a major risk factor for recurrence.[183]

Previous ATE

These patients have a higher risk of embolism than patients without previous episodes. Therefore, the period of sub-therapeutic anti-coagulation should be kept to a minimum. In patients whose INR is 2.0–3.0, it takes 4 days for it to spontaneously fall to < 1.5, an intensity of anti-coagulation at which increased intra-operative bleeding is not expected after anti-coagulation is stopped. Therefore, 4 daily doses of warfarin should be withheld preoperatively, and the INR should be measured the day before surgery to determine if a small dose of vitamin K is needed to accelerate the reversal of anti-coagulation:

(1) In general, give 1 mg of vitamin K by slow i.v. injection if the INR is > 1.7 the day before the surgery, repeat the INR the morning of surgery.

(2) If necessary, fresh frozen plasma (FFP) can be given prior to surgery if the INR is still not acceptable (i.e., INR 1.3–1.7, 1 FFP unit, 1.7–2.0, 2 FFP units). Administration of blood products should generally be avoided for elective surgery.

No previous ATE

The risk after discontinuing anti-coagulation is lower in patients who have not had a previous episode. Warfarin can be withheld for 5 doses to ensure that coagulation has returned to normal prior to surgery; however inpatients with prosthetic heart valves have a higher risk of thromboembolism. In these patients, i.v. unfractionated heparin should be substituted while warfarin (alternatively LMWH therapeutic schedules may be used) is withheld till INR < 1.3, then heparin is withheld 1 to 2 hours (short half-life) prior to surgery. As the usual intensity of anti-coagulation is higher in such patients, a small dose of vitamin K is required more often in these patients on the day before surgery.[183]

Last episode of ATE within 1 month

The risk of recurrent ATE is highest within a month of an acute event (about 0.5% per day). To minimise the possibility of preoperative embolism, i.v. heparin should be administered when INR drops to < 2.0. Stopping i.v. heparin 6 hours prior to surgery should be adequate for the aPTT to return to normal before surgery.[183]

(b) Venous indications for anti-coagulation

The main indication for anti-coagulation is prevention of recurrent VTE. An exception occurs in selected patients with patients with thrombophilia (e.g., anti-thrombin, protein C, protein S deficiencies, FV Leiden abnormalities, and strong family history of thromboembolism).[183]

Last VTE event within 1 month

The risk of recurrent VTE declines rapidly with duration of anti-coagulation. There is a very high risk of recurrent VTE if anti-coagulants were stopped within 1 month of VTE. Therefore, if feasible, surgery should be deferred until patients have received 1 to 3 months of anti-coagulation. If this is not feasible, preoperative thromboembolic risk should be minimised by administering i.v. heparin when INR is less than 2.0.

Last VTE between 1 to 3 months

These patients have a moderately high risk of recurrent VTE if anti-coagulants are stopped. Warfarin should only be withheld for 4 doses to minimise this period of high risk.

Last VTE > 3 months

These patients have a much lower risk of recurrent VTE than those who have been treated for < 3 months.

Postoperative

Start warfarin as soon as possible

If coagulation has previously returned to normal, there will be 2–3 days delay after warfarin is restarted before the INR begins to increase. Thus warfarin should be restarted as soon as possible after surgery in all patients who do not have additional invasive procedures planned. In patients who are having a minor procedure associated with a low risk of bleeding, warfarin can be restarted shortly before surgery.[183]

Previous ATE within 1 month of minor surgery

The risk of recurrence is sufficiently high within a month of acute ATE that i.v. heparin is warranted until the INR reaches 2.0, provided the risk of bleeding is not very high. Heparin should be started 12 hours after surgery.[182]

Previous ATE within 1 month of major surgery

Despite a high risk of recurrence while the INR sub-therapeutic, heparin should be avoided shortly after major surgery as the risk of bleeding will likely outweigh the anti-thrombotic benefits. Unfractionated heparin or LMWH given in doses recommended for VTE prophylaxis of high risk patients is safe and should be given until the INR reaches 1.8.

No previous ATE within 1 month of surgery

This includes patients without previous ATE and those with ATE that has occurred more than a month previously. S.C Heparin should be given at prophylactic dose.

Postoperative VTE

Surgery is a major risk factor for VTE, and the risk of thrombosis is much higher postoperatively than it is preoperatively. Therefore, the greater need for thromboprophylaxis postoperatively.

Recommendation on the reversal of oral anti-coagulant treatment by the British Committee for Standardisation in Haematology[182] in managing bleeding episodes related to warfarin are:

1. *Life-threatening haemorrhage*
   Immediately give vitamin K (5.0 mg) intravenously slowly and either a concentrate of factor II, IX, X with factor VII (if available) or fresh frozen plasma.
2. *Less severe haemorrhage, e.g., epistaxis or haematuria*
   Withhold warfarin for one or more days and consider giving vitamin K (0.5–2.0 mg) intravenously slowly.

3. *INR > 4.5 with no haemorrhage*
   Withhold warfarin for 1 or 2 days, then review.
4. *Unexplained bleeding at therapeutic levels*
   Investigate for underlying cause, e.g., renal or alimentary tract abnormality.

SURGERY IN PATIENTS WITH BLEEDING TENDENCY

Inherited coagulation disorders

von Willebrand's disease

vWD is the most common hereditary haemostatic disorder, this is associated with reduction in von Willebrand factor (vWF) quantity or function resulting in defective platelet adhesion and because vWD is the carrier molecule for VIII, low factor VIII clotting activity. The inheritance is autosomal dominant with varying expression. vWD is usually of mild to moderate severity (easy bruising, mucous membrane bleeding, epistasis, menorrhagia), prolonged bleeding following minor injury or surgery, but in the rare homozygous form, patients suffer haemarthroses and muscle haematomas.

The condition is diagnosed by a combination of the clinical findings supported by abnormal laboratory tests (depending on the type) including, prolonged bleeding time, prolonged aPTT, low factor VIII clotting activity, defective ristocetin induced platelet aggregation, low vWF antigen, and ristocetin cofactor activity. Patients with a mild phenotype respond to Desmopressin (DDAVP), while more severe ones require factor VIII concentrate, which contains vWF. Specialist input from a haemophilia centre should be sought as early as possible if surgery or other procedures were anticipated.

Haemophilia A (factor VIII deficiency)

Haemophilia A (HA) is inherited as an X-linked recessive disorder, but 33% of cases arise as a result of spontaneous mutation. It affects 1 in every 10,000 males. Patients with severe HA (VIII < 1% of normal) suffer from recurrent spontaneous painful haemarthroses and muscle haematomas with progressive deformity and crippling, if not

adequately treated. Haemophiliac pseudotumours may occur in long bones from repeated sub-periosteal haemorrhage with bone destruction, new bone formation, expansion of the bones and pathological fractures. Patients with moderately severe and mild disease may have severe post-traumatic bleeding.

Diagnosis in suspected patients is established by specific laboratory tests including prolonged aPTT, low factor VIII clotting activity, normal vWF level, and normal bleeding time.

Bleeding episodes are treated with factor VIII concentrates (plasma derived or recombinant) or in milder cases Desmopressin (DDAVP), which lead to a temporary rise in factor VIII due to release from the vascular endothelium. An anti-fibrinolytic agent (e.g., tranexamic acid) should also be given because Desmopressin also induces vascular release of t-PA.[184]

Haemophilia B (factor IX deficiency) (Christmas disease)

The inheritance and clinical features of factor IX deficiency are similar to those of Haemophilia A. The incidence is about 1 in every 50,000 males. The diagnosis is established by demonstrating low levels of Factor IX clotting activity in a patient with suspected deficiency and prolonged aPTT, normal bleeding time. Bleeding episodes are treated with factor IX concentrate (plasma derived or recombinant).[184]

Haemophilia and surgical procedures

With proper care most procedures can now be carried out on haemophiliacs. The risk of any procedure is, however, greater than for someone with a normal factor VIII level, and the risks and the benefits of the procedure should be carefully evaluated and any alternatives considered. Lack of communication is a source of major problems and steps should be undertaken to prevent this. For this, a written plan should be documented in the patient's notes. This may subsequently be revised and any amendments to the plan should also be documented.[184]

For specific therapy and perioperative management, the haematologist in charge of the haemophilia centre should be involved.

Confirm the diagnosis of haemophilia, ascertain if an inhibitor is present or not, and ascertain the previous recovery levels in response to DDAVP. Is this the patient's first exposure to blood products? If so, virological surveillance tests are required. Explain to the patient the risks and the benefits. Has the patient received hepatitis B vaccination? Any additional problems, e.g., thrombocytopenia in HIV infected patients or abnormal liver function tests (and, therefore, prolonged PT).[184,185]

Intermediate and Major Procedures

Plan of management

Should include:

Type of concentrate to be used (or DDAVP).
The initial level required to cover surgery.
The duration of treatment required (the exact frequency of treatment will have to be managed on an *ad hoc* basis).
Need for tranexamic acid.
Frequency of monitoring and exact timing in relation to surgery.

Perioperative management

Give the FVIII approximately 90 minutes before the planned operation time.
Take pre- and post-infusion levels.
Except for minor procedures, take a "fall off" level 4 hours postoperatively to plan further replacement therapy.

Postoperative management

After major procedures the FVIII level should not be allowed to fall below 50% for at least 10 days.
Beyond the immediate postoperative period treatment is determined by FVIII half-life (12 hours), therefore, 12-hourly infusions to 100% levels is satisfactory.
Frequent measurement of levels is very helpful as there is a tendency for them to drift either up or down.

Any postoperative procedures, such as, removal of drains or physiotherapy should be timed to follow shortly after FVIII administration.

A period of once daily treatment, which may be given at home may be necessary in some patients. Its duration should be judged from the nature of the procedure and the need for any further treatment, such as, physiotherapy.

Minor procedures

Some minor procedures require only a single dose of FVIII to approximately 60%, unless problems arise. This can be used in the following procedures:

Skin biopsy and minor skin surgery
Endoscopy
Straightforward dental extraction
Liver biopsy:

The transjugular approach is the preferred method in patients with bleeding disorders in general.

HAEMOSTATIC ALTERATION IN CARDIOPULMONARY BYPASS SURGERY

Open cardiac surgery produces significant activation of coagulation, fibrinolysis, and platelets, despite the use of heparin. This is due to the presence of the cardiopulmonary bypass circuit. The following are well-documented alterations.[186]

1. **Platelet defects during CPB:** A qualitative platelet abnormality exists in virtually 100% of patients during CPB and usually reverses within an hour or so after completion of CPB. The blood-material surface interaction and shear effects of flow through the circuit traumatise platelets. CPB produces thrombocytopenia, platelet fragmentation, and platelet function abnormalities, including a reduced response to aggregation stimuli. This is due to discharge of alpha granules and loss of platelet membrane receptors, such as, GpIb and GpIIb/GpIIIa. As P-selectin is expressed on the inner

surface of α-granules, their release produces increased platelet surface expression of P-selectin. Activated platelets are also able to bind leucocytes forming polymorphonuclear- and monocyte-platelet conjugates. The degree of impairment in platelet function correlates with the duration of CPB and with the level of hypothermia. The defect occasionally persists longer and sometimes results in bleeding. The level of hypothermia used during the procedure and contact with the synthetic surface of the oxygenator contribute to the haemostatic defect. Moderate hypothermia (28–32°C) is used during CPB to reduce tissue ischaemia and preserve the myocardium. This affects platelet number and function. The generation of thrombin-antithrombin (TAT) complexes is greater during and after hypotheremic bypass compared to normothermic bypass. Postoperative blood loss and transfusion requirements also appear to be greater in patients undergoing hypothermic CPB.[195]

Transfusion of platelet concentrates promptly controls the bleeding. Despite abnormalities in platelet number and function, there is no evidence that routine perioperative transfusion of

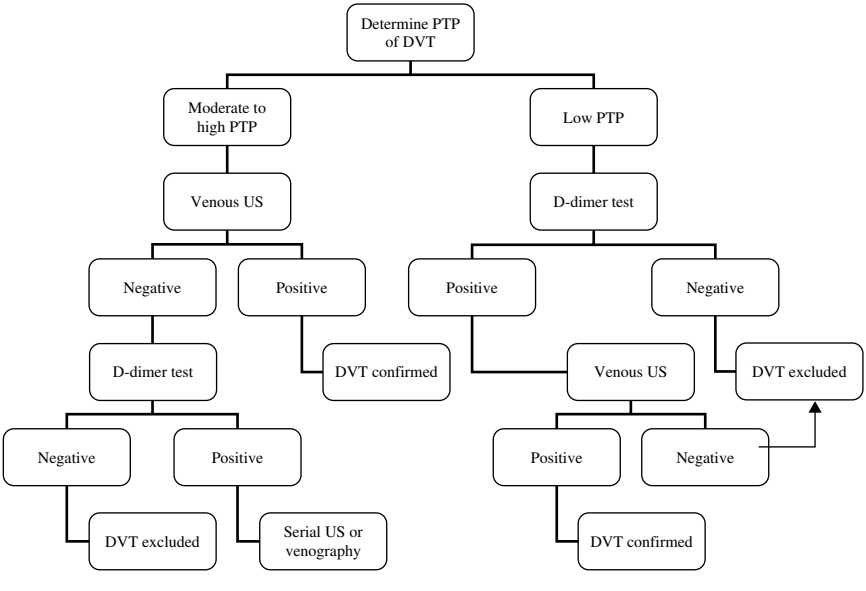


Fig. 14 Algorithm for diagnosing DVT based on clinical assessment of pre-test probability (PTP), venous ultrasonography (US), and d-dimer testing.

platelet concentrates is necessary (Office of Medical Application of Research, National Institute of Health, UK Health Department 1989). Many patients with coronary artery disease may be taking aspirin. Patients taking aspirin before CPB surgery are at risk of excessive blood loss during the procedure. It is, therefore, recommended that aspirin be discontinued 5 to 10 days before CPB surgery.[186,187]

2. **Thrombocytopenia:** Platelet counts after bypass are generally between 50 and 150 $\times$ 10^9/l.

   Thrombocytopenia itself is rarely a cause for postoperative bleeding.
3. **Failure to neutralise the heparin completely is rarely seen with modern techniques.** Use of thrombin time (TT) and reptilase time quickly clarifies the presence of excessive heparin. Following initial adequate heparin neutralisation, the re-appearance of active heparin in the circulation may occur 2 to 6 hours later. This rebound effect is caused by the delayed return of sequestered extravascular heparin, which occurs when peripheral perfusion improves.[186]
4. **DIC:** This does not occur regularly during the CPB procedure. In the postoperative period, DIC occurs uncommonly and usually reflects other problems, such as, poor cardiac output, acidosis, and sepsis.
5. **Fibrinogenolysis:** Activation of fibrinolysis measured by D-dimer levels has been shown to peak during CPB. There is a wide variation in fibrinolytic response to CPB. The increased fibrinolytic activation is mainly due to an increase in t-PA and to lesser extent by contact activation that is maximal at the first passage of blood through the extracorporeal circuit. Some of the t-PA is released from the coronary circulation after cardioplegic arrest has been performed. During CPB the peak of TAT levels precede high D-dimer levels, suggesting the majority of t-PA released is from the endothelium secondary to thrombin generation. One study showed that peak D-dimer levels correlate with postoperative bleeding. Recent studies indicate that fibrinogenolysis is much less frequent during bypass than previously believed and probably accounts for bleeding uncommonly. Nonetheless, if the euglobulin clot lysis time is shortened and there is no evidence of DIC, judicious use of tranexamic acid sometimes dramatically halts bleeding.[186,188,189]

6. **Activation of coagulation during CPB:** Despite systemic heparinisation, CPB produces significant activation of coagulation compared to other thoracic operations not requiring CPB. The thrombogenic effect of the extracorporeal circuit is the main stimulus with surgical cutting playing a lesser role. The time course of activation of coagulation show a significant increase on initiation of CPB and a rapid fall at the end of CPB. CPB surgery is associated with a drop in the plasma levels of most coagulation factors, which is primarily attributable to haemodilution. As with platelet concentrates, it is not necessary to routinely transfuse FFP during CPB. Inappropriate use of FFP in CPB surgery is common and has logistic and economic implications.[190] Selective deficiency of high molecular weight von Willebrand factor multimers and associated prolongation of bleeding time with haemorrhagic tendency have been described in both adults and children with valvular heart disease or congenital cardiac defects. Surgical correction of the defect results in normalisation of the multimer pattern.[186]
7. **Haemodilution:** Is a consequence of extracorporeal circulation, but the fall in haematocrit, platelet count, and plasma proteins including coagulation factors is about 25 to 30%. Therefore, it is not sufficient to cause bleeding.

Determinants of haemostasis in CPB

Given differences in bleeding rates and definitions of what is normal, excess bleeding can probably be defined as > 1 litre per procedure. There is twice the risk of bleeding after valve surgery than after CABG, and repeat operations redouble this risk; significantly, 19% of CABG patients need re-grafting within 10 years. Bleeding is usually manifest postoperatively, after protamine reversal of heparin, and shed from the operative field into mediastinal and pleural drains. If aspirin or other anti-platelet therapy has been given, the operation may be "wet" from the start.[191–193]

Critical rates of blood loss, formulated by Kirklin and Barrett-Boyes,[194] are:

500 ml in the first postoperative hour,
400 ml/h in the first 2 hours,

300 ml/h in the first 3 hours,
1 litre in 4 hours, or
1.2 litre in 5 hours.

If bleeding attains these rates, is acute and massive, or begins again after ceasing, resternotomy becomes unavoidable. Volume *per se* can mislead if there is progression from blood to serosanguinous drainage; the haematocrit of the fluid in the drain tubing (not the reservoir) may indicate that blood loss is being overestimated if the patient is otherwise stable.

The need for re-sternotomy entails 30% increase in perioperative mortality and, therefore, is a crucial endpoint in CPB studies. In 67% of cases bleeding vessels are found, often small medistinal arteries or the aortotomy incision; such vessels might not bleed if haemostasis were normal. In the remainder, general microvascular oozing is seen.[195]

Allogeneic RBC transfusion post-CPB shows wide, apparently irrational, variance between centres. Some centres transfuse RBC to fewer than 1/3 of standard risk CPB patients, others to more than 2/3 despite access to evidence-based guidelines, with similar inconsistency in platelet and fresh frozen plasma use.[196–201]

Withholding RBC unless the systemic haematocrit fell to < 25% (Hb < 8g/dl), post-CPB, had no adverse clinical or physiological impact in standard-risk patients. Observing this threshold is likely to reduce allogeneic transfusion. The role of cardiac surgeons and anaesthetists in UK hospital transfusion committees will be vital as a means of audit and effective guidelines in this area.[196–201]

Preoperative determinants of haemostasis in CPB:[191–193]

1. Bleeding increases if aspirin continues up to surgery. This effect is eliminated if aspirin is stopped 7 days before and restarted 1 to 6 hours after surgery. If aspirin cannot be stopped, haemostasis should be enhanced by anti-fibrinolytic therapy.
2. The calcium antagonist nimodipine was associated with excess post-CPB bleeding in one report.
3. Coumarin anti-coagulants (e.g., in transplantation when a donor heart arrives too suddenly to omit warfarin) require replacement

therapy with prothrombin complex concentrate (PCC) containing factor VII if INR > 1.7.

4. Coronary angioplasty/stenting with the hybrid anti-GpIIb/IIIa monoclonal agent abciximab (c7E3, ReoPro) may need urgent conversion to CABG. Intra- and postoperative bleeding occurs, particularly if the interval between abciximab and CPB is < 12 hours or if standard doses of heparin are used for CPB. Reducing heparin (to ACT 400s) with postoperative (± preoperative) platelets is one approach. Others suggest aprotonin with platelet transfusion (6 units) given at the end of the bypass. True and pseudo-thrombocytopenia can occur after abciximab therapy and must be distinguished from heparin-induced thrombocytopenia.
5. Patients with congenital heart disease may acquire a deficiency of high-molecular weight von Willebrand's factor, which rarely poses a problem, as it corrects immediately post-surgery. Right-to-left shunts can lead to increased platelet size with misleading automated counts (check the blood film). Children with Noonan syndrome may have coagulation factor deficiencies and can bleed during surgery for heart defects; they need a haemostatic work-up before cardiac surgery.[191–193]
6. Patients with haemophilia may require CPB; the safest operative cover in all cases is high-purity or recombinant factor VIII:C or IX:C. In von Willebrand's disease a product with a reliably high content of high-molecular-weight multimers should be used. All such patients should be managed at centres with comprehensive expertise in haemophilia.[191–193]
7. Preoperative thrombocytopenia compounds the bypass-induced platelet function defect. The minimum acceptable preoperative platelet count is 100×10^9/l. In patients with ITP, administration of steroids and or IVIG might be required.[191–193]

MODIFYING PERIOPERATIVE BLOOD LOSS

Continued concerns over the risks of using allogeneic blood, especially those of transfusion-transmitted infection, combined with occasional shortage of donor blood and increasing costs (with the

introduction of universal leucodepletion in the wake of variant-CJD), have stimulated interest in perioperative blood conservation. Two broad approaches to blood conservation have been pursued. The first is to accept that blood loss is inevitable and to use measures to conserve patients' blood. Measures, such as, autologous blood predeposit have received increasing interest as have the use of autotransfusion, the venesection of one unit prior to CPB and reinfusion of residual oxygenator blood after bypass, the use of cell savers, and the acceptance of a normovolaemic anaemia postoperatively. These measures have been poorly applied in the UK mainly because of the high cost associated with formal programmes. The second approach to blood conservation is to prevent blood loss at the time of surgery by using pharmacological methods.[202]

Perioperative bleeding

Excessive bleeding can be due to surgical causes (i.e., suture deficiency) and/or derangement of haemostasis. The most important determinant of surgical blood loss is the surgeon. There is a subset of patients, however, in whom generalised oozing in the surgical field cannot be attributed to demonstrable bleeding vessels.

No consensus exists for the pathogenesis of non-surgical perioperative bleeding. There are several reasons for this: (1) failure to appreciate the limitations of laboratory tests; (2) shortcomings in the current concepts of haemostasis; and (3) lack of reliable laboratory tests for some components of haemostasis, e.g., fibrinolysis.

Pharmacological agents to reduce blood loss

(1) ***Anti-fibrinolytics***[203–219]

Aprotinin: Is a potent anti-fibrinolytic agent. Its molar potency *in vitro* is 100- and 1000-times of tranexamic acid and epsilon amino-caproic acid (EACA). It directly inhibits kallikrein production and, therefore, activation of plasminogen by factor XIIa and indirectly inhibits t-PA release by bradykinin inhibition. Aprotinin can also mop up any plasmin by its direct powerful anti-plasmin action. Aprotinin inhibits activated Protein C, which is formed during CPB. Aprotonin is a bovine protein and, therefore, can provoke an immunological reaction.

The most dramatic reductions in perioperative blood loss have been associated with the administration of aprotinin. Royston *et al.*,[203,204,208] gave a high dose aprotinin regimen in patients undergoing "repeat" cardiac surgery. Postoperative drainage loss was reduced by 81%, total haemoglobin loss by 89%, and mean blood transfusion requirement was reduced by 91%. Further clinical studies have confirmed that high-dose aprotinin dramatically reduces blood loss after CPB. Shorter operating times are also seen in children, a probable consequence of the fact that the operative fields remain "bone dry".

It is widely used in Europe including the UK. It is licensed for use in high risk cases, but most cardiac surgeons are reluctant to use it in first time CABG. This is due to the theoretical (but unproven) prothrombotic effects and the potential for the patient to develop anti-aprotinin antibodies that would prohibit their use in future surgery. The use of recombinant protein analogous to human protease nexin II has shown some efficacy in a sheep model.[203] The majority of users of aprotinin in the UK do not use the full high-dose regimen, to reduce cost, and in the recognition that a lower dose does reduce bleeding, although possibly not to the same extent.[208]

Aprotinin has no effect on the fall in platelet count, but may have a minor effect on preserving platelet function by preserving platelet membrane receptors, possibly by inhibiting plasmin-mediated degradation. All trials have shown that there is a profound inhibition of fibrinolysis, suggesting that its main mechanism of action is through an anti-plasmin effect. The success of other anti-fibrinolytics in reducing bleeding supports this mechanism.[203]

(2) *Other anti-fibrinolytic agents*

Lysine Analogues: When plasminogen and plasmin bind to fibrin it is thought their lysine-binding sites. In the presence of lysine analogues epsilon amino-caproic acid (EACA) and tranexamic acid, the binding is reduced and fibrinolysis delayed.[210–216]

EACA has been used successfully in the control of bleeding due to hyperfibrinolysis following transurethral resection, but others found no significant benefit in patients undergoing cardiac surgery. In one randomised study on patients undergoing CABG, tranexamic acid reduced the blood loss in the first 10 hours by a third.[215]

Desmopressin acetate or DDAVP:
It is a synthetic vasopressin analogue that is relatively devoid of vasoconstrictor activity. It increases the plasma concentration and activity of vWF probably by inducing its release in the endothelium. vWF mediates platelet adhesion to damaged endothelium and also to act as a carrier molecule for factor VIII;C. Plasma levels of vWF increase 2- to 5-fold from the baseline within an hour and are associated with a shortening of the bleeding time in patients with von Willebrand's disease, platelet function defects, and uraemia.[188] Two studies of patients undergoing "re-do" cardiac operations showed that 0.3 mg/kg of DDAVP given after CPB reduced blood loss, elevated vWF levels, and shortened bleeding times.[188] In three trials using DDVAP in doses 0.3 mg/kg after the termination of CPB in uncomplicated CABG, the changes in plasma levels of vWF were studied. In the control group there was a doubling of vWF level and a greater rise in levels of vWF in the DDAVP treated group. This was, however, not accompanied by enhanced platelet aggregation or increased functional activity compared with the placebo treated group. The blood loss was similar. To conclude, it appears that DDAVP is not beneficial in uncomplicated CABG patients.

DDAVP increases the release of t-Pa from the endothelial cell, and this may reduce the beneficial effects of increasing vWF.

(3) *Fibrin sealants*

The sealants mimic the final part of the coagulation cascade in that a source of thrombin is added to the fibrinogen concentrates in the presence of calcium and a clot forms. Fibrin glue has been used to secure haemostasis in patches and suture lines during congenital heart surgery. In one retrospective study, it reduced blood loss significantly. There is no licensed fibrin sealant in the US or UK, but they are available on a named patient basis. Initially, thrombin was of bovine origin, which led to the development of a bleeding diathesis postoperatively, due to the formation of cross-reactive antibodies to bovine thrombin that inhibit factor V. Despite extensive clinical experience with fibrin sealants, the data available is mainly descriptive and randomised clinical trials are needed to fully assess

their contribution to reducing bleeding. The other concern, as with any other product produced from plasma, is transfusion-transmitted diseases. Methods for producing autologous fibrin sealants are, however, being evaluated.[220]

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Haemostasis in Neurosurgery

Peter Bullock and Roopen Arya

INTRODUCTION

In surgery there is a fine balance between bleeding and thrombosis. Although the haemostatic process helps to halt excessive blood loss it might, in a prothrombotic milieu, become pathological and lead to thrombosis. In the management of surgical patients, it is essential to minimise the risk of complications from bleeding. Perioperative bleeding in the neurosurgical setting may have devastating consequences and lead to blindness or paralysis. Hence the importance of meticulous haemostasis in all cranial and spinal operations. In addition, neurosurgical patients are at a risk of thromboembolism.[1–3] Symptomatic deep vein thrombosis (DVT) is recorded in 20% of patients in the absence of any thromboprophylaxis. Fatal pulmonary embolism (PE) is reported in 1.5% to 5% of neurosurgical patients. A risk assessment of bleeding versus thrombosis must be performed preoperatively in every neurosurgical patient to ensure an optimum outcome. This permits the early use of prophylactic measures thus reducing the risk of thrombosis and bleeding.

Neurosurgery is unique in that postoperative bleeding can be devastating and result in death or disability. As a consequence absolute haemostasis is essential. Technical advances such as the operating microscope and bipolar coagulation allow the accurate control of bleeding from fine cortical vessels. Chemical haemostasis also plays a part in the control of bleeding from capillaries and veins. However unlike his colleagues in other specialties the neurosurgeon can rarely rely on drains to an operative site or use monopolar coagulation.

It is important to recognize that the brain also contains a higher concentration of thromboplastin than any other human tissue. The liberation of thromboplastin into the circulation institutes the extrinsic clotting cascade. Sufficient thromboplastin activation can be a factor in patients developing disseminated intravascular coagulation after a severe head injury. The triggering of the extrinsic cascade is also likely to be a factor in the development of vasospasm seen in patients after subarachnoid haemorrhage.

PREOPERATIVE ASSESSMENT

A comprehensive medical history is important to identify patients at risk of bleeding.[4] Significant factors include a family history or the patient suffering bleeding after previous surgery or dental extractions. One study indicated that a positive medical history is much more likely to predict bleeding than any laboratory test. Other significant symptoms may include epistaxis, menorrhagia and or bruising. However von Willebrand disease may be clinically silent and may only manifest itself in situations of stress, such as an operation. A detailed drug history of prescribed medication and alternative medicines is vital.

Haemostatic screening tests, including the platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen are routinely requested when major intracranial or spinal surgery is considered. A platelet count identifies patients with thrombocytopenia, but does not detect platelet dysfunction. In neurosurgical patients, platelet counts of 100×10^9 or more are required to reduce the risk of bleeding complications. The PT is a measure of the extrinsic coagulation pathway and reflects the procoagulant

activity of factors II, VII, IX and X. Common causes of prolonged PT are warfarin, liver disease, and vitamin K deficiency. The APTT detects disorders of the intrinsic pathway, such as, the haemophilias or von Willebrand disease (VWD) though may be normal in some cases of mild haemophilia or VWD. Common acquired causes of prolonged APTT include unfractionated heparin and the presence of a lupus anticoagulant. Unlike unfractionated heparin low molecular weight heparins do not reliably prolong the APTT, and anti-factor Xa assays are required if monitoring is necessary. The most common cause of prolongation of both PT and APTT is disseminated intravascular coagulation (DIC). In DIC, D-dimers are usually raised and, in later stages, fibrinogen levels are reduced. Anyone suspected of a bleeding disorder should be referred to a haematologist for assessment so that screening tests might be performed together with specialised investigations. These tests may include bleeding time and coagulation factors assays. Platelet function studies using the platelet function analyser (PFA-100^{TM}) or the platelet aggregometer may also be performed.

Drugs are a common cause of bleeding and a history of relevant medication is essential.[5] The drugs that need to be considered include anticoagulants, anti-platelet drugs, and non-steroidal anti-inflammatory drugs. Commonly used anticoagulants include warfarin, unfractionated heparin, and low molecular weight heparin.[6] Warfarin should be discontinued prior to neurosurgery. Perioperative anticoagulation will be determined by the indication for anticoagulation. In low-risk patients, warfarin is discontinued four days preoperatively, and no bridging anticoagulation is required. Patients at high risk such as those with recent history of thromboembolism or those with mechanical heart valves require appropriate cover with either unfractionated heparin or low molecular weight heparin, when they are off the warfarin. Intravenous unfractionated heparin may be stopped four hours preoperatively, but due to its longer half-life, the last dose of low molecular weight heparin should be at least 24 hours before neurosurgery. On the day of surgery, clotting studies have to be repeated to ensure that values are within acceptable levels.

Anti-platelet agents have widespread use in patients with arterial disease and increase haemorrhagic risk in patients undergoing

surgery. The most commonly used agent is aspirin (acetylsalicylic acid), which acts by irreversibly inactivating the enzyme cyclooxygenase-2 for the life of the platelet. Aspirin should be stopped at least seven days prior to surgery to enable platelets to develop, unaffected by irreversible cyclooxygenase inhibition. Non-steroidal anti-inflammatory drugs (NSAIDs) should be stopped at least two days preoperatively to enable the restoration of any reversible cyclooxygenase inhibition they may cause. The new generation of NSAIDs, the cyclooxygenase-2 inhibitors, such as, rofecoxib or celecoxib do not significantly affect platelet function. Clopidogrel, which blocks platelet ADP receptors, is increasingly being used for secondary prevention of myocardial infarction and cerebrovascular accidents. Like aspirin, the anti-platelet effect is irreversible and lasts the lifetime of the platelet. Therefore, discontinuation of the drug 7 to 10 days preoperatively, is essential. Dipyridamole, however, reversibly inhibits phosphodiesterase and may be discontinued only 24 hours before elective surgery.

The advent of aggressive anti-thrombotic treatment as adjuvant to angioplasty or stent placement has increased the risk of haemorrhage associated with these procedures. Glycoprotein IIb/IIIa inhibitors include abciximab, eptifibatide, and tirofibran. Abciximab, a chimeric monoclonal antibody, was the first drug of its class to be developed. Platelet aggregation is almost completely inhibited two hours after treatment is begun and recovery is evident by 48 hours after treatment discontinuation. Mild thrombocytopenia develops in 5% patients and severe thrombocytopenia in 0.7% patients receiving abciximab. In a meta-analysis, major bleeding occurred in 2.4% patients (versus 1.4% placebo). Intracranial bleeding was rare, however, occurring in 0.12% patients as opposed to 0.09% patients receiving heparin alone. A higher rate of intracerebral haemorrhage seems to be associated with neurointerventional procedures than with coronary interventional procedures. This is likely to be related to recent cerebral ischaemic events and reperfusion injury.

When a patient taking anti-platelet agents presents for emergency neurosurgery, and the drug has not been discontinued, platelets should be transfused even if the platelet count is normal. In the anticoagulated patient who requires emergency neurosurgical

intervention, for instance, after intracranial haemorrhage, complete reversal of anticoagulation would be indicated.[7] If the patient is taking warfarin, a vitamin K antagonist, immediate administration of intravenous vitamin K would be required. Since this takes several hours to be effective, prothrombin complex concentrate (PCC), a virally inactivated plasma product rich in vitamin K dependent coagulation factors, should also be administered. PCC are associated with a small risk of thrombosis and should be avoided in patients with previous history of ischaemic heart disease or thromboembolism. In these patients, fresh frozen plasma (FFP) may be used for immediate reversal of the warfarin effect. In patients receiving unfractionated heparin, coagulation should return to normal within a few hours after discontinuation, due to the short half-life of the heparin; protamine may also be used as an antidote. With low molecular weight heparin the half-life is approximately 18 hours, and only a fraction of the anticoagulant activity may be reversed by protamine. The new generation of anticoagulants, including pentasaccharides, oral direct thrombin inhibitors, and oral anti-Xa inhibitors, do not have a specific antidote.[8] If intracranial bleeding occurs, the use of recombinant factor VIIa may be considered in addition to the usual haemostatic measures such as infusion of FFP.[9]

Neurosurgery may be required in patients with inherited coagulation defects.[10] This might be for intracranial haemorrhage due to the bleeding disorder or for treatment of other pathology that has coincidentally occurred in such a patient. In these patients it is essential to work closely with the haematological team to establish the correct diagnosis and define the haemostatic risk preoperatively. The most common bleeding disorders are von Willebrand disease and haemophilia A and B. In those with haemophilia a preoperative inhibitor screen is vital to ensure a predictable and satisfactory response to infused factor concentrate. Factor levels should be maintained in the neurosurgical patient as high and long as appropriate. The prescribed factor is infused prior to the surgery, and the factor level is measured before induction of anaesthesia to ensure an appropriate level, usually 100% preoperatively. Continuous infusion of factor concentrate is used increasingly in preference to bolus doses, providing smoother pharmacokinetics and reduced

consumption of factor.[11] Factor levels must be monitored twice daily initially and then daily to ensure appropriate factor dosage and adequate haemostasis.

INTRA-OPERATIVE TECHNIQUES

Successful surgical outcomes depend upon a clear diagnosis and careful planning. Vascular tumours should be reviewed with the interventional neuroradiologist so that feeding vessels can be identified pre-operatively and if appropriate occluded by glue or coils using endovascular techniques. This can reduce blood loss as well as the length of the operation.

As a consequence of studies such as the International Subarachnoid Trial (ISAT) endovascular techniques are becoming increasingly important. The majority of cerebral artery aneurysms are currently being treated by the endovascular route with soft platinum coils rather than by an open operation to clip the aneurysm (Fig. 1). Aneurysms with wider necks and often more complex morphology

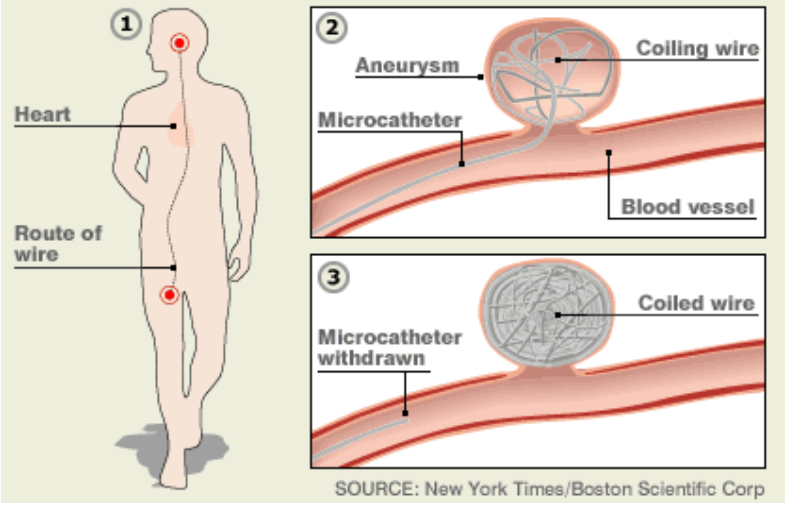

Fig. 1 Coiling. Endovascular coiling of aneurysms is frequently the method of choice for the treatment of aneurysm. This prevents rupture and further bleeding from the aneurysm.

may not be suitable for coiling and therefore still require clipping. In this situation temporary clips may be applied to the feeding vessels for a short period of time. Rarely it is necessary to provide a bypass to essential vessels to repair giant non-clippable aneurysms. In this group of patients a bypass anastomosis can be fashioned in a number of ways. The ELANA technique (excimer laser-assisted non-occlusive anastomosis) is a novel and reliable technique to fashion the anastomosis between the external and internal carotid arteries.[12] In general, lasers are not regularly used in spite of their early promise.

Proximal control is essential in procedures that may require direct approach to an intracranial aneurysm or an invasive skull base tumour. There should be a clear understanding between surgeon and anaesthetist about the potential blood loss before starting any operation. Central, peripheral and arterial lines are routine. Cranial surgery on an infant should start only once the cross-matched blood has been verified and ensured to be available.

The approach to lesions that are known to be vascular, such as, arteriovenous malformations, meningiomas, or haemangioblastomas should involve preoperative consultation with an interventional neuroradiologist. Temporary aneurysm clips may be used in the situation of an unexpected severe arterial blood loss whilst the intravascular volume is restored. Temporary clips may be safely left on any major artery for two to three minutes, to allow time for dissection of the adjacent structures. A clock is started as soon as the clip is applied and the time counted out. Placing vascular clips blindly into an area of rapid bleeding is rarely, if ever successful. Adequate exposure with brain retractors and suction is essential, so that the surgeon can see and determine the origin of the bleeding. This aspect is in line with other forms of surgery, where adequate exposure and patience remains paramount. In neurosurgery one cannot pack the brain, and the area of applied pressure should be as small as possible. Adequate visualisation can often be accomplished with patties and two suckers. It is not usually possible to sacrifice intracranial or spinal vessels, and they may need to be repaired with fine sutures. In this respect, neurosurgery differs from other surgical specialities. Rapid excision of a tumour with surrounding brain is rarely an effective haemostatic technique and is likely to lead to a major neurological deficit. The

skill of the surgeon, the position of the lesion, the type of lesion, and the condition of the patient are some of the variables that have to be considered in the risk-benefit equation. Unfortunately, unlike surgery in other areas of the body, closing a bleeding wound over a drain in intracranial surgery is not an option if the patient is to make a useful recovery. The judgment, to take some risk by increasing the speed at which a lesion is removed, is something not easily learned and depends on many variables. A rapid enucleation of a tumour with a finger is not acceptable.

Blood pressure may be decreased as a temporary measure to control bleeding but has a limited role in neurosurgery and can lead to irreversible brain damage because of the reduced cerebral perfusion. Profound hypothermia and cardiac bypass have been employed to access and repair giant cerebral artery aneurysms but these approaches were often complicated by disturbances of clotting and have not proved popular in comparison to the recent advances in endovascular techniques. The period of time and the extent of induced hypotension that can be employed to control bleeding are dependent on the age of the patient and the presence of associated vascular disease.

In certain circumstances a large volume of blood can be unexpectedly lost from venous bleeding. The sagittal sinus may be opened unintentionally during the turning of the bone flap or resection of an invasive meningioma. The elevation of a depressed bone fragment from the sagittal sinus can also cause major loss of blood. This potential loss can be anticipated and avoided by careful review of the preoperative skull X-rays. One approach to control venous bleeding, whether it is accidental or anticipated, is to consider what would be necessary if the opening were deliberate and planned. The first step is to obtain the necessary exposure and all the borders defined by extending the bone work. The rule that adequate exposure is required, applies to all forms of surgery. Local pressure with surgicell, patties, and wet mastoid swab (with elevation of the head) are usually sufficient to control the venous bleeding, whilst the bone is removed. Cannulation of the venous sinus may be considered necessary, using a small Foley catheter to occlude the lumen by distending the balloon. Only the proximal third of the sagittal sinus can be sacrificed

without risk of cerebral infarction. Balloon occlusion of the distal sinus may be temporary, until a decision can be taken on whether the opening can be approximated directly or requires grafting. An assistant is invaluable at this time to control the suction and enable stepwise exposure of the defect involved. A free pericranial flap can be used to graft the defect and maintain patency, but in the majority of cases haemostasis is successful with local tamponade from layers of surgicell and local pressure. A Foley catheter occlusion or a vascular shunt may need to be used if the repair requires considerable time and the defect is difficult to control with local pressure.

In contrast to bleeding from a tumour or a vessel, generalised bleeding from exposed surfaces suggests a coagulopathy, either pre-existing to operation or acquired during the operation. It is always difficult to stop an operation and study a problem. Most surgeons have a tendency to continue operating and simply request that the clotting studies be repeated. If the bleeding is deep and could cause compression or displacement of the brain, the surgeon may not have the choice of stopping without endangering the patient. Both situations require laboratory studies to determine the cause, but a surgeon should always remember that uncontrolled or continued bleeding is most often caused by lack of effective local haemostasis rather than by a coagulopathy.

INSTRUMENTATION FOR HAEMOSTASIS

Haemostasis must be achieved in all phases of the surgery. It is important to gain haemostasis in the superficial layers before proceeding to the deeper structures. In a craniotomy plastic haemostatic "Raney" clips are first applied to the edge of the scalp. The bone edges are waxed and then the extradural space is closed with hitch sutures. The dura can then be opened and the operative field is kept clear and dry for working under the microscope. Complex cranial and spinal operations often take four hours or longer and continuous blood loss can jeopardise a patient's haemodynamic status if there is continuous oozing.

Bipolar coagulation is fundamental to neurosurgery because it enables precise coagulation of small vessels without dangerous spread

of the current to adjacent neural and vascular structures.[13] A range of bipolar forceps of different sizes and lengths should be available. A larger tip, 2 to 3 mm, is necessary to control bleeding from the scalp margins. Finer tips, 0.3 to 1 mm, can be used on or within the dura. The bipolar forceps also need to be of different lengths. Bayonet lengths with 8 cm shafts are suitable for working on the brain surface. Blades measuring 9.5 cm are suitable for coagulation of deeper structures, such as, around the circle of Willis, and 11 cm blades may be necessary for trans-sphenoidal operations. Bipolar instruments are continually being revised. Bipolar tips can be self-irrigating, and any rise in impedance can be monitored to prevent charring and sticking of the tips of the forceps. Irrigation is essential to prevent this charring. It is important to reduce the current setting when switching from a standard bipolar to the fine tips, for microsurgery. The narrower the forceps tip, the higher will be the current density for the same amount of current flow. The interface between the forceps tips and the tissue should be wet with continual irrigation of saline. In bipolaring vessels, the tips should be kept slightly open. The forceps should not be simply closed over the vessel as this will lead to short-circuiting and no coagulation occurs (Fig. 2).[14] At sites where even gentle coagulation could result in neural damage, such as around the optic or acoustic nerves, an attempt is made to control the bleeding with lightly applied haemostatic material. *Surgicell* (an oxidised regenerated cellulose), *gel foam* (a gelatinous sponge), or *avitene* (a microfibrillar collagen) may be used. Floseal matrix haemostatic sealant, a gelatine matrix, is expanding its range of use. It has been found to be a reliable if not expensive agent to control bleeding in both cardiac and spinal surgery.[15]

Cutting loops or ultrasonic aspirators are routinely used for tumour removal. They do not control bleeding although some are designed to enable coagulation to be applied through the tip. Tumours of the brain or spinal cord are often removed piecemeal unlike cancer surgery where the tumour is excised intact. The external capsule is first devascularised and then the tumour mass is emptied before the tumour is delivered. Removal of a tumour is invariably piecemeal and bipolar coagulation provides the ability to achieve precise haemostasis without causing damage to the surrounding neural structures.

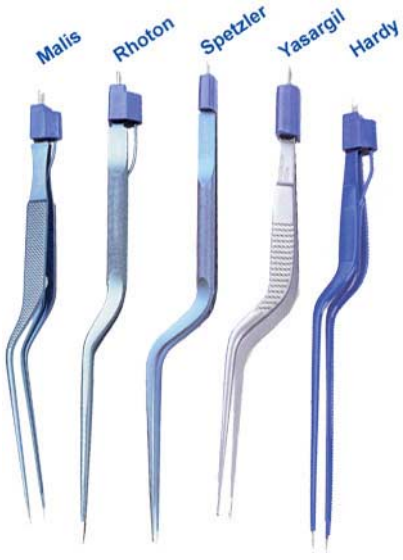

Fig. 2 Forceps. The provision of properly shaped and balanced bipolar forceps has been undertaken by a number of neurosurgeons. The forceps are angled to stay out of the line of vision. There is a range of lengths and the polished tips vary in size. The bipolar forceps are used with constant saline irrigation.

POSTOPERATIVE HAEMATOMA

Postoperative complications from intracranial haematoma are uncommon after elective brain surgery and rare after elective spinal surgery (< 3%). The principles of meticulous haemostasis and avoidance of dead spaces are common to both cranial and spinal surgery in preventing postoperative haematoma.[16] The larger the craniotomy flap, the greater is the risk of a haematoma. This risk increases significantly with emergency trauma surgery because of the wider area of damage.

The potential space under a large bone flap was identified as a significant risk factor in 59 patients who developed postoperative haematoma that required evacuation. Most of these postoperative haematomas were extradural. These 59 patients were from a total number of 850 patients who were admitted with severe head injuries and had intracranial haematoma evacuated. Factors predisposing to a recurrent haematoma included high alcohol intake, brain atrophy,

coagulopathy and initial intradural bleed. These injuries and major surgery may consume platelets and clotting factors. Alcohol itself is known to be a cause of thrombocytopenia, and there may also be sub-clinical liver damage. Patients with significant postoperative haematomas, most commonly, deteriorate within 24 hours of surgery. The haematomas seen can reflect bleeding at the craniotomy site in either the intradural or extradural spaces due to inadequate surgical haemostasis at the initial procedure or may reflect other factors, such as, a coagulopathy. Therefore, before any re-operation, the full clotting profile must be reviewed. The incidence of haematomas is also dependent upon the criteria used to make the diagnosis. Routine postoperative CT brain scans often demonstrate an accumulation of blood under the bone flap. Generally, this collection does not cause any mass effect or shift and will resolve without evacuation. Patients with severe head injuries routinely undergo a second CT brain scan 24 hours after admission because of the risk of rebleeding from existing surface contusions that can enlarge, coalesce, and re-bleed causing local mass effect.

Extradural haematomas, after both elective and emergency craniotomies, can be prevented by attention to securing haemostasis at all stages of the operation. The scalp edges are secured before the bone flap is fashioned. After the bone flap is elevated, haemostasis is secured in the extra-dural space and hitch sutures (tacking sutures) placed around the edges of the bone margins. These tacking sutures should only go through the outer layer of the dura. If the suture goes through the full thickness of the dura, the cortex or cortical vessels may be injured and result in a subdural haematoma. In large craniotomies, the extradural space can be reduced further by tacking the centre of the dural flap to the middle of the skull flap (Poppen suture). Titanium liga clips are routinely used to control bleeding from the dural edges.

There is an overall risk of at least 1% for postoperative haematomas, after elective neurosurgery. There is however considerable variation in incidence for different pathologies and different ages. Brain tumours can pose intra-operative and postoperative difficulties with haemostasis. The highest incidence of postoperative haematoma after surgery for intracranial tumours is seen in the

elderly, particularly after the excision of a meningioma. On an average, 7% of patients over 70 years of age require re-operation for evacuation of a haematoma that usually occurs in the tumour bed. This compares to 2% incidence of evacuated postoperative haematoma in patients undergoing surgery for intrinsic tumours. Coagulopathy and thrombocytopenia are recognised as general risk factors. Size, location, or histological subtype of the meningioma did not influence the risk of postoperative bleeding. The other potential factors such as dural sinus invasion, extent of tumour resection and degree of tumour vascularity did not influence the overall risk of a postoperative haematoma. Why age on its own influences the risk of a postoperative haematoma has not been fully answered. Changes in the blood vessels and poor platelet function have been suggested. There are also the structural factors with brain atrophy and failure of the brain to re-expand. In addition the elderly may have a different clotting profile after surgery, compared with younger patients who have a higher risk of thrombocytopenia. Open operations are routine for extrinsic tumours, but intrinsic tumours such as gliomas are often deep and situated in eloquent areas. Therefore a stereotactic biopsy is the safest approach. The risk of bleeding from this blind procedure is less than 2% and is again related to the vascularity of the tumour as well as the other general risk factors. It is of interest that there is no statistically significant difference of haematoma formation between stereotactic procedures for tumour biopsy and functional procedures (e.g. implantation of deep brain electrodes to control tremor).

Neurovascular surgery has undergone considerable revision in the last decade, with less open procedures being followed. Today, neuroradiologists undertake the majority of interventional procedures for aneurysms and AVMs. These endovascular procedures routinely use intravenous heparin during the interventional procedure. Bleeding can occur if the aneurysm ruptures during manipulation of the guide wire or placement of the coil. In these situations, the aneurysm is rapidly packed with further coils, and protamine may be used to reverse the heparin. The overall risk of complications from bleeding is 2%. Emergency ventricular drainage for obstructive hydrocephalus may be required soon after coiling of an aneurysm. This carries an

increased risk of intra-parenchymal bleeding because of the presence of the heparin.

The outcome of patients with postoperative intracranial haematomas is poor. Death occurs in 15% of the cases, and 40% are left with significant disability. The management of postoperative haematoma will depend on the location of the haemorrhage and the presence or absence of any symptom. Subgaleal scalp haematomas are best left to resolve on their own, without aspiration. Repeat aspirations are likely to introduce infection. The recognition and management of symptomatic intracranial haematomas generally require an urgent response. At the first signs of neurological deterioration, a CT brain scan is requested to exclude other causes for the patients' clinical condition such as brain swelling. In certain circumstances, when there is no time for the CT scan, it may be appropriate to make the diagnosis on clinical grounds and take the patient directly to the operating room. Irreversible damage can occur if the condition is not recognised promptly. Extradural haematoma should be suspected in any patient who develops a new postoperative neurological deficit.

In a case of a symptomatic progressive extradural haematoma, immediate evacuation is essential. If a coagulopathy is present, it should be corrected in consultation with the haematology service. Post-craniotomy patients with a coagulopathy, who have no symptoms or signs of an emerging haematoma, are closely monitored. It is preferable to correct the coagulopathy before it causes haemorrhage, rather than treat the haemorrhage.

NON-SURGICAL MANAGEMENT OF PERIOPERATIVE BLEEDING IN NEUROSURGERY

There are two main causes of perioperative bleeding. The first, surgical bleeding is due to a failure to surgically control bleeding vessels at the operative site and has been discussed earlier in this chapter. This bleeding usually occurs at a single site and is confined to the operative field. Physical measures, such as, pressure, liga clips, tamponade, or diathermy are required to control blood loss. Non-surgical or haemostatic bleeding, on the other hand, results from a failure of haemostasis. This might be due to pre-existing undetected

bleeding disorder or massive blood transfusion. Additionally it may be caused by haemostatic abnormalities secondary to the surgery. Often, it results from a combination of pathologies. There may be associated hypothermia, acidosis and hypovolaemia. There may be evidence of generalised bleeding and oozing and manifestations of disordered haemostasis including petechiae, purpura, and oozing from venepuncture sites, central venous catheter sites, urinary catheters, and nasogastric tubes.

In this setting, there are several components to the management of bleeding. It is essential to identify high-risk patients preoperatively. In many of these instances measures such as discontinuation of relevant medication or appropriate blood product cover preoperatively, will substantially diminish operative bleeding risk. An understanding of perioperative haemostatic changes is also essential. This may be related to the underlying pathology as well as the consumption of coagulation factors, platelets, and natural anticoagulants that follow significant blood loss. Massive blood transfusion constitutes blood loss that requires the replacement of the complete blood volume in less than 24 hours. In such a situation it is vital to monitor the full blood count and coagulation tests regularly and transfuse the appropriate blood products. It is usually necessary to transfuse appropriate doses of packed red cells, FFP (15 ml/kg), and platelets to ensure haemostasis. Platelet counts should be kept above 100×10^9 in the neurosurgical setting. If fibrinogen levels are low (less than 1.0 g/dl) transfusion of cryoprecipitate should also be considered. Hypothermia must be avoided as a fall of body core temperature may result in deranged coagulation.

Pharmacological interventions may also be used for prevention and treatment of perioperative bleeding.[4,17] These agents may improve primary haemostasis, stimulate fibrin formation, or inhibit fibrinolysis. Anti-fibrinolytic drugs include aprotinin and lysine analogues such as tranexamic acid. The haemostatic effects of these agents depend upon inhibition of fibrinolysis as well as, in the case of aprotinin, a protective effect on platelets. Aprotinin is a 58 amino acid polypeptide of bovine origin, which directly inhibits various serine proteases, including plasmin. Adverse effects are rare but hypersensitivity reactions have been reported including anaphylaxis. The use

of aprotinin is contraindicated in disseminated intravascular coagulation and in patients with renal failure. Aprotinin's usefulness has been demonstrated in various surgical settings, particularly cardiac surgery and liver transplantation where prospective studies show significant decrease in bleeding and transfusion requirements. The efficacy and safety of the aprotinin has also been established in patients having intracranial surgery. In a study of 100 patients requiring surgery for an intracranial meningioma or a vestibular schwannoma, intra-operative blood loss was halved by the use of prophylactic high dose intravenous aprotinin. Although there is a theoretical risk of increased thrombosis with the use of prohaemostatic agents, in clinical practice thrombotic complications are rare. Local haemostasis may also be improved by the use of fibrin sealants, which usually consist of a thrombin source added to fibrinogen concentrates in the presence of calcium. This mimics the final steps of the physiological clotting cascade to form a fibrin clot. The use of these topical agents is now well described in neurosurgery. They reduce local blood loss and incidence of CSF leaks. In patients with severe bleeding unresponsive to conventional measures, recombinant factor VIIa may help achieve haemostasis.[9] This haemostatic agent was developed from our understanding of the key role of tissue factor/factor VII in activating the coagulation pathway *in vivo*. Recombinant factor VIIa acts primarily via a tissue factor-dependent mechanism that limits its action to the site of bleeding, although some tissue factor-independent effects may also be involved, particularly on the platelet surface. There are anecdotal reports of successful use in neurosurgical and trauma patients, but the role of this costly therapy remains to be defined.

The use of near patient testing enables a convenient and dynamic global assessment of haemostasis in surgical patients.[4] One of the main methodologies is thromboelastography (TEG), which is a dynamic viskokinetic monitoring device that analyses whole blood coagulation and fibrinolysis parameters. It provides sequential information about initial clot time, clot strength, and the degree of fibrinolysis. A study of TEG in neurosurgery patients has demonstrated progressive hypercoagulability over the course of surgery. This begins with induction of anaesthesia and increases over the course of surgery with the most dramatic increases during the early stages and, then,

after tumour removal or aneurysm clipping. In this small study, young females who underwent craniotomy were the most hypercoagulable. In addition to defining global haemostasis, TEG may be used to optimise blood product support in bleeding patients, perioperatively. Another near patient device finding increasing utility in evaluating haemostasis in the surgical setting is the platelet function analyser (PFA-100^{TM}).

RISK OF THROMBOEMBOLISM IN NEUROSURGERY

Neurosurgical patients and in particular those with spinal injuries and brain tumours are prone to venous thromboembolism (Fig. 3). Laboratory tests are of limited use in identifying those in a prothrombotic state. It is more important to identify the multiple risk factors contributing to thromboembolism. In the neurosurgical patient with a brain tumour these can include impaired mobility and the use of procoagulants such as steroids, chemotherapeutic and hormonal agents. Furthermore tumours themselves are believed to secrete procoagulant factors such as tissue factor and fibrinolytic inhibitors.

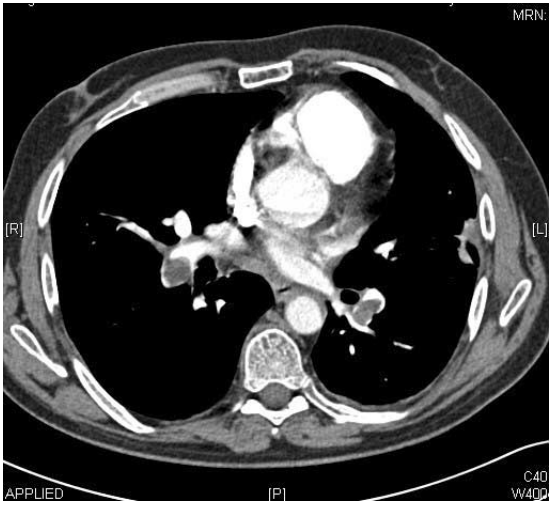

Fig. 3 Helical CT of the pulmonary arteries with intraluminal filling defects diagnostic of pulmonary embolism.

The measures that are used are still based on the notion that venous thromboembolism is a consequence of trauma to the vessel wall, stasis and hypercoagulability as first described by the German physician Rudolf Virchow.

THROMBOPROPHYLAXIS IN ELECTIVE NEUROSURGERY

The high incidence of VTE in neurosurgery patients makes the use of thromboprophylaxis mandatory.[2,18] Even a small intracranial bleed might have devastating consequences and therefore a rational thromboprophylactic strategy incorporating both mechanical and pharmacological measures is essential. These measures are often simple such as ensuring that the patient is well hydrated and mobile and that unnecessary arterial and venous cannulae are avoided. The use of mechanical measures, such as, intermittent pneumatic compression (IPC) and graduated compression stockings (CS) help reduce thrombotic risk by minimising reducing venous stasis and dilation. In addition local fibrinolysis is stimulated with a reduction in plasminogen activator inhibitor and an increase in circulating endogenous tissue plasminogen activator. IPC appears to be highly effective at preventing DVT in neurosurgery patients with an average risk reduction of 68% compared with controls (Fig. 4). Although one study revealed

Fig. 4 Intermittent pneumatic compression is highly effective at preventing deep vein thrombosis in neurosurgical patients.

that CS alone was as effective as the CS and the IPC combination, concerns about the efficacy of CS alone have been raised. Two large prophylaxis studies have compared the use of CS alone, with a combination of CS and LMWH started within 24 hours postoperatively. With CS alone DVT rates were 26% and 33%, respectively, improving to 19% and 17% using combined prophylaxis. However, we must be cautious about preoperative or early postoperative LMWH prophylaxis in craniotomy patients, as intracranial haemorrhage rates in randomised trials were 2.1% for postoperative LMWH and 1.1% for mechanical prophylaxis or no prophylaxis. Most bleeds occurred within the first two days after surgery. Furthermore, in a meta-analysis examining VTE prevention in neurosurgery, all forms of bleeding were twice as common in those receiving LMWH postoperatively as opposed to mechanical measures (6.1% versus 3.0%; $p = 0.02$).

In summary, IPC with or without CS is currently recommended for VTE prevention in patients undergoing intracranial neurosurgery. In high-risk neurosurgery patients, a combination of mechanical prophylaxis and pharmacological prophylaxis may be considered. If used, LMWH or low dose UFH should be given postoperatively. The former is more convenient and has a lower incidence of side effects such as heparin induced thrombocytopenia. Individual circumstances and assurance of secure postoperative haemostasis will determine the timing of commencement of prophylaxis. If the patient is at a high bleeding risk, for instance, due to recent ingestion of anti-platelet drugs, pharmacological prophylaxis may be withheld and commenced later in the postoperative course. In patients weighing less than 90 kg, the dose of LMWH should not exceed 40 mg of enoxaparin or dalteparin 5000 units, daily. On occasion, use of smaller doses or split dosing can diminish bleeding risk. Extended thromboprophylaxis should be considered in high-risk patients, including those with malignancy, thrombophilia, and prolonged immobility. The use of surveillance duplex ultrasonography may also enable early detection of a DVT. There is no role for anti-platelet agents, such as, aspirin in prophylaxis of venous thromboembolism.

Patients with acute spinal cord injury have high VTE rates, with symptomatic DVT and PE rates of 15% and 5%, respectively.[2] PE remains the third most common cause of death in these patients.

Mechanical measures alone are insufficient, and pharmacological measures must be instituted. LMWH is more effective than low dose or adjusted dose UFH in this setting, but initiation must be delayed if there is evidence of perispinal haematoma. Patients with spinal cord injury remain at risk of thrombosis for at least three months, particularly if the injury is complete. Extended thromboprophylaxis would be indicated using LMWH or warfarin aiming for a target INR of 2.5.

TREATMENT OF VENOUS THROMBOEMBOLISM (VTE) IN NEUROSURGICAL PATIENTS

Commonly VTE follows neurosurgery, but surgery might occasionally be required in patients with a recent VTE.[19] Diagnosis of VTE is based on algorithms incorporating clinical probability, D-dimers, and imaging (such as duplex ultrasound for DVT and spiral CT or ventilation-perfusion scans for PE). D-dimers, the smallest degradation product of the fibrin clot, are useful because they have a high negative predictive value. In the postoperative setting, however, when D-dimers are quite often raised, their utility is limited. Duplex ultrasonography has largely replaced venography as the imaging of choice and convenience to diagnose DVT, but sensitivity for pelvic and calf vein DVT is sub-optimal. CT with pulmonary angiography has replaced ventilation-perfusion scanning as the imaging of choice for PE, due to higher sensitivity and specificity and the ability to demonstrate alternative diagnoses if PE is excluded. In future, magnetic resonance imaging (MRI) is likely to be increasingly important for diagnosis of DVT and PE.

After VTE has been diagnosed, conventional therapy comprises once daily LMWH injections and warfarin.[20] The LMWH is usually given for at least five days and discontinued when the INR is within the therapeutic range. Below-knee DVT is usually treated for three months and proximal DVT or PE for six months. In the neurosurgical setting, therapy will depend on risk of bleeding in the individual patient together with the timing and the location of thrombosis. In the immediate postoperative period, systemic anticoagulation is best avoided due to risk of intracerebral bleeding. Remote from this period, patients should be cautiously anticoagulated. If there is still a

concern about the risk of bleeding then intravenous UFH may be used in the first instance, aiming for an APTT ratio at the lower limit of the therapeutic range. The advantage of this approach includes the short half-life of the heparin together with the availability of an antidote in protamine. An alternative approach is the initial use of split doses of LMWH ensuring smoother anticoagulation control, with lesser peaks and higher troughs. If monitoring is required, due to concerns about bleeding risk, anti-factor Xa levels may be measured. LMWH is as efficacious as UFH in the treatment of DVT and submassive PE and is more convenient, with the use of once or twice daily subcutaneous injections without routine monitoring. Adverse effects such as heparin induced thrombocytopenia and osteoporosis are reduced. In the bleeding patient, however, it must be remembered that LMWH's anticoagulant effect lasts 18 to 24 hours and protamine will reverse only a fraction of this.

When anticoagulation is contraindicated, vena caval filters are an important alternative (Fig. 5).[21] The primary purpose of implanting

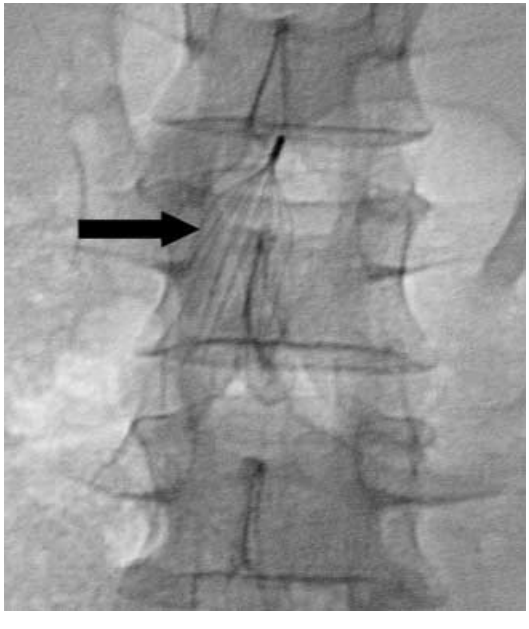

Fig. 5 Vena cava filters prevent pulmonary embolism in patients with deep vein thrombosis who have a contraindication to anticoagulation.

a vena caval filter is to prevent a potentially fatal PE. A high complication rate has, however, been seen in brain tumor patients with VTE treated with IVC filter. In a small study of 42 patients, 12% experienced recurrent PE and 57% developed IVC or filter thrombosis, recurrent DVT or post-phlebitic syndrome. When IVC filters are used there is a significant decrease in early PE, but a higher incidence of recurrent DVT in the long-term. Therefore, IVC filters should only be used in selected neurosurgery patients, to enable us to withhold anticoagulation during the period of maximal bleeding risk. At other times, anticoagulation remains the best option. The availability of new generations of retrievable IVC filters provide a valuable tool for the treatment of DVT in neurosurgical setting as the contraindication to anticoagulation is only temporary. These filters can often be retrieved many weeks after insertion, following which the patient can be anticoagulated as usual.

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Haemostasis in Otorhinolaryngology and Head and Neck Surgery

Julian A. Gaskin and Kalpesh S. Patel

INTRODUCTION

Haemostasis is defined as the stopping of a flow of blood.[1] In all areas of surgery it is essential to achieve haemostasis to prevent complications, such as haemorrhage that may lead to shock and death or haematoma that may lead to infection and wound dehiscence.

In preparing any patient for surgery it is essential that a full preoperative history has been taken. It is of vital importance that information, such as bleeding disorders or a family history of bleeding disorders, is determined. In a recent study it was found that of the patients who developed postoperative bleeding complications, around 90% could have been avoided if a preoperative history of bleeding disorder had been recognised. The study also reported that such failures constituted a major public health problem.[2] Other

important preoperative information is whether the patient is receiving anti-platelet or anti-coagulant therapy (such as, aspirin, dipyridamole, or warfarin) and when or if this has been stopped.

EAR

The achievement of haemostasis in otological surgery is essential for the operation to proceed. This is due to the small scale of the microscopic work taking place. Often, under magnification, a small amount of bleeding can disrupt the surgeon's operative field to such an extent that the procedure may have to be abandoned.

One of the main techniques used to maintain a clear operating field in microscopic ear surgery involves close partnership with the anaesthetist, who can achieve a low operating blood pressure. By allowing the patient to be anaesthetised safely in a hypotensive state, the otologist obtains a drier field in which to operate. Any bleeding that occurs during this period should be immediately recognised and stopped before the whole area becomes engulfed with blood. Other techniques employed to achieve a bloodless field in ear surgery include the use of adrenaline (epinephrine). This is often used initially with a local anaesthetic, such as lidocaine, to inject the subcuticular tissues prior to the skin incision. Adrenaline is also used to saturate tiny cotton wool pledgets that can be placed down the ear, over sites of bleeding to stop or slow oozing, helped with the element of compression. An adrenaline-soaked cotton ball is often an adjunct, albeit an important adjunct, to the use of bipolar diathermy for specific bleeding points.

Studies have looked into the effects of hypotension during ear surgery. It is widely recognised that hypotension is a useful technique to improve the operative field in ear surgery, under the microscope. However, the way this is achieved has been debated. The use of sodium nitroprusside is just one example of how a powerful antihypertensive has been trialled in such cases. One study using nitroprusside found it to be problematic, causing frequent tachyphylaxis, and not showing any greater effectiveness over commonly used anaesthetic techniques.[3] Another study, however, revealed potential benefits with platelet aggregation.[4]

NOSE

Epistaxis is common. Treating and managing such patients comprises a large proportion of the ENT clinician's practice. Bleeding from the nose affects a wide range of age groups and presents different challenges. The very young, trauma victims, and elderly patients are all at risk. It is often helpful to categorise bleeding from the nose by site, into anterior or posterior. Anterior bleeding often arises from the highly vascular Little's area of the nasal septum. This area represents the most accessible area for administering treatment.

Bleeding from the nose can be initially controlled by compression. This forms a part of the triad of techniques called Trotter's manoeuvre, designed to stop epistaxis. The techniques are compression, sitting forwards, and cold compress application (to the head). Experience has shown that after 10 to 15 minutes most nose bleeds will have settled. If evidence of a bleeding point is seen, either with anterior rhinoscopy or using a rigid endoscope, it may be possible to administer chemical (i.e. silver nitrate) or electrical cautery to the offending vessel. This can be done under local anaesthesia and particular forms, such as cocaine solution or phenylephrine would also assist via their vaso-contrictive properties.

If there is failure to achieve haemostasis or a bleeding point cannot be found, packing of the nose may be required. Many intra-nasal packing devices, such as Merocel® and Rapid Rhino® packs are available. If, despite all these techniques haemostasis is still not achieved, probably the best type of pack is ribbon gauze. It is impregnated with the antiseptic and haemostatic properties of bismuth iodoform paraffin paste (BIPP), and if placed well will fill the contours of the nasal cavity (see Fig. 1).

Almost all epistaxis can be controlled with a well placed BIPP pack, which may or may not be needed in conjunction with a posterior balloon. This balloon usually takes the form of a catheter device passed along the floor of the nasal cavity to the nasopharynx, inflated with water or air, retracted slightly to block the posterior choanae, and fixed in this position under tension. Prophylactic antibiotic cover should be given with posterior packing.

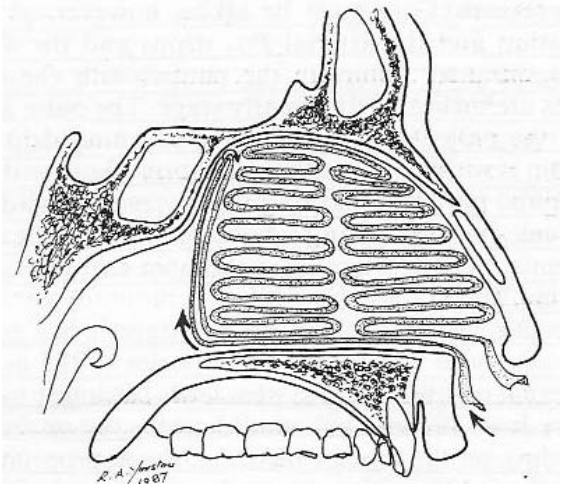

Fig. 1 Logan Turner's diseases of the nose, throat, and ear.

If this type of packing does not control the haemorrhage, despite a safe period of observation, then surgical intervention may be required. This can take the form of a septoplasty and/or artery ligation. It has been postulated that a deviated nasal septum contributes to mucosal erosion and, therefore, a predisposition to bleeding on the deviated side. Following septoplasty, the resulting fibrosis created after raising the muco-perichondrial flaps may also help in reducing troublesome vascularity of the septum. Artery ligation can take the form of sphenopalatine, ethmoidal, or maxillary depending on the site of bleeding in the nose. Sometimes, the external carotid artery may need to be ligated to stop a difficult maxillary artery bleed (see Fig. 2).

It is important to mention that as radiological techniques have improved, further treatment options have come to the fore. This includes embolisation to achieve haemostasis. In head and neck cases, especially trauma victims, potentially life-threatening haemorrhage from deep vessels may require significant or prolonged exploration, under a general anaesthetic, by expert head and neck vascular surgeons. Angiographic embolisation of bleeding vessels has been shown to be an alternative to head and neck exploration.[5] Embolisation plays a role not only in trauma, but has also been used in patients with

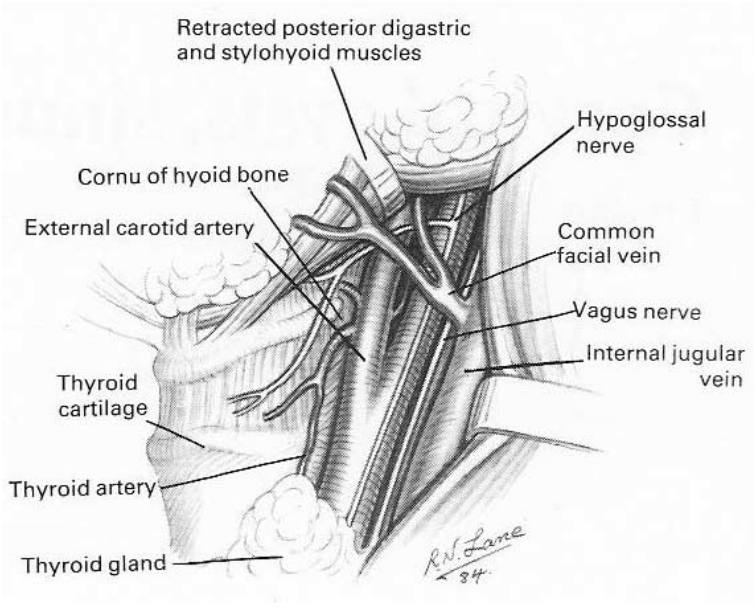

Fig. 2 Rob and Smith's operative surgery — nose and throat.

bleeding from vascular malformations and tumours. In addition, it has been used in patients with aneurysmal bleeds.[6]

HEAD AND NECK

Tonsillectomy is probably the most common surgical procedure in otorhinolaryngology. Yet, the best way to achieve haemostasis in this procedure is often debated by surgeons. Pressure with plain packs or packs soaked with a haemostatic agent are used. Ice has also been used over the tonsillar beds after resection. In addition, ties have been used to ligate specific bleeding points. Other methods using electrical means include mono-polar, bi-polar, and coblator diathermy. Instrumentation, such as, harmonic scalpel, have also been tried.[7] The most important technique, and the one used by probably all surgeons, is the haemostatic, pause. The act of waiting for several minutes and relaxing the pressure applied to the tissues aids in clotting and haemostasis, or discovering smaller bleeding points prior to completion. Early results of a national audit into tonsillectomy showed that the most

used technique in tonsillectomy haemostasis is bipolar diathermy. The technique which produced the lowest proportion of primary or secondary haemorrhage after dissection, however, involved the use of ties alone.[8]

Another relatively common head and neck procedure undertaken is thyroidectomy and parathyroidectomy. Significant postoperative complications are bleeding and haematoma formation. The reason a haematoma is of particular concern with these procedures is the close anatomical relation to the trachea, with the potential of airway obstruction due to compression.

Head and neck cancers often pose difficulties in resection — not least due to the challenges of the anatomy in that area, with significant neurovascular structures. With poorly differentiated or invasive tumours here, the risk of damage to these structures is increased. Sometimes, this occurs as a part of a patient's presenting symptoms, for example, hoarseness (in recurrent laryngeal nerve palsy). The external carotid artery may also be at risk, and the term *carotid blow-out* refers to haemorrhage from the carotid artery, usually from erosion by an invasive neck carcinoma. It is almost impossible to gain haemostasis from such a haemorrhage. When these events occur, bleeding is so profuse that even if it occurs in hospital, resuscitation is commenced immediately. The patient is rushed straight to theatre, and the time involved in this is probably enough for the patient to have exsanguinated. If the patient is operated on, tying off the external carotid artery is the only chance of stopping the haemorrhage, to gain haemostasis (see Fig. 2). Unfortunately, patients who suffer such an event are the ones who are aware of their terminal diagnosis and may have undergone a debilitating course of chemotherapy or radiotherapy.

Apart from malignant causes, trauma is another cause of head and neck haemorrhage. Most likely to occur in the young adult age group, trauma may be divided into blunt or penetrating. Mechanisms can be through accidents, road traffic accidents, assaults, stabbings, gunshot injuries, sporting injuries, and falls. Haemostasis, as with haemostasis of malignant origin, can be difficult to achieve. Significant structures can be damaged due to the major vessels carried in the neck. As

opposed to oncology cases, however, the anatomical structures may be much less distorted than in a large destructive invasive squamous cell carcinoma for example.

Any attempt to ligate bleeding vessels should always be carried out in a controlled environment, with a clear operating field. As mentioned earlier, apart from major vascular structures, major nerves are also present in the neck. Important nerves include the vagus, phrenic, and laryngeal nerves. Structures, such as, the trachea, oesophagus, and thyroid gland also have to be identified. This may be simple in elective procedures, but in emergency operations with significant haemorrhage, the picture may be completely different. Electrical tools, such as diathermy, to aid in haemostasis may cause thermal damage to these structures as well as damage caused by misplaced ligatures.

Embolisation, as mentioned earlier, can be a very useful therapeutic tool in controlling bleeding arising from the head and the neck. Principles and specific clinical applications of its use in the head and the neck have been considered. One study's results, for example, revealed not only good haemostasis, but the reduction of tissue mass and pain relief in malignant cases.[9]

Other strategies trialled include the use of vasopressin as a continuous infusion. Results showed haemostasis was established quickly in 80% of the cases, with no serious side effects. Therefore, its apparent beneficial effects could provide an alternative to external carotid artery ligation.[10]

CONCLUSION

Haemostasis plays a large and important role in otorhinolaryngology and head and neck surgery. It requires different techniques used on different areas of the head and neck. Whatever technique required, most procedures would be unable to be completed without adequate haemostasis. Certainly, postoperative complications would be high in the absence of effective haemostasis. New advancements in techniques and technology are enabling new ways to achieve haemostasis, adding to the surgical options available.

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Haemostasis in Cardiac Surgery

Shirish G. Ambekar and Brian Glenville

Haemostasis is a process that involves various molecular reactions. These reactions have evolved for the basic purpose of preservation of life. The body's natural mechanisms come into play to limit blood loss after trauma. Many sequential and overlapping events occur in the body, including vasoconstriction, formation of platelet plugs, and activation of coagulation cascade. Simultaneous activation of the complement system and fibrinolysis also help to maintain the delicate balance and to restore the *milieu interior*. An understanding of these events and other methods of haemostasis is important in any faculty of surgery, more so in cardiac surgery.

In cardiac surgery, it is essential to understand the haemostatic process for two reasons. First, most of the patients undergoing cardiac surgery receive heparin, which is a strong inhibitor of coagulation cascade. As we intervene externally into the natural mechanism of haemostasis, we also need to know the ways to reverse the actions on the coagulation cascade. The action of heparin is reversed by protamine, which forms electrostatic complexes with the molecules

of heparin. This blocks heparin's action on different steps of the cascade. Second, the incisions on the heart and the surrounding structures need be closed in such manner that they restore the blood-tight compartments. Technological advances in sutures and needle manufacturing have made major contributions in this respect. In addition, the development of new drugs and glues and topical agents like cellulose, gelatin, thrombin, and fibrinogen have also benefited surgery.

HISTORICAL NOTE

Till the early 20th century, the scope of cardiac surgery was restricted to the repair of cardiac trauma and the closed heart procedures for rheumatic valvular lesions. There was an urgent need to be able to stop the heart without causing damage to the vital organs and to perform surgery for pulmonary embolus and cyanotic heart disease. This had to wait until the discovery of heparin. Heparin was first discovered in its impure form in liver tissues, by the research fellow, Jay McLean and Professor Howell from John Hopkins Institute, Baltimore. It gained its name from the word "Hepatic", because it was extracted from liver tissues. After the discovery of insulin by a team from the University of Toronto, Charles and Scott from the same team succeeded in extracting a pure form of heparin in 1929, at the University of Toronto. Dr. Gordon Murray, a thoracic surgeon from Toronto used this heparin in experimental animal models and proved its efficacy as a strong anti-coagulant. In 1949, when Dr. Maloney and Dr. Taylor received a patent for their improved method of heparin production,[1] heparin became available commercially in a purified form.

Heparins have variable molecular weight depending on their source and have been shown to give rise to thrombocytopenia in some cases. The problem of heparin induced thrombocytopenia (HIT), was partly addressed by the discovery of low molecular weight heparins (LMWH) that later replaced heparin in the use of deep vein thrombosis prophylaxis and in the treatment of unstable angina.

Protamine was discovered from a whale sperm in the early 20th century. At the University of Toronto, it was initially used as an agent to prolong the duration of action of insulin. Due to a strong positive

charge on its molecules, it was thought that protamine would form electrostatic complexes with heparin and, therefore, prolong the duration of action of heparin. In fact the reverse was true, and it was discovered that protamine could act as a reversal agent for heparin by preventing its action on the coagulation cascade.

In 1937, Gibbon of Philadelphia first published an account of cardiopulmonary bypass (CPB) in the cat. He was able to clamp the pulmonary artery for 25 minutes, while bypassing the blood with an assembly of pumps and an oxygenator.[2] As World War II intervened, Dr. Gibbon had to wait until 1953 to publish his first successful open heart surgery.[3] As cardiac surgery spread rapidly across the world, it was soon realised that the bubble oxygenators used were the main source of blood injury and inflammation. Kolff and Balzer were the pioneers in reducing this problem. They worked on animals, successfully using a coil dialyser as an oxygenator.[4] By 1958 Clowes *et al.* were able to report clinical use in adults, although it required large membrane area to support necessary gas exchange.[5]

Along with heparin and protamine other pharmacological agents, in particular, Aprotinin also made significant contributions towards haemostasis following cardiac surgery. Aprotinin is a naturally occurring protease inhibitor isolated from bovine lung tissue. It was independently discovered by Kraut *et al.* in 1930[6] and by Kunitz and Northrup[7] in 1936. It was found to be able to inhibit Kallikrein and Trypsin. In the 1970s, Aprotinin was first used in pancreatitis as an anti-inflammatory agent, but soon its use was appreciated in cardiac surgery, as an agent reducing blood loss. Later, the mechanism was seen to be due to its action on wider scale on the pathways of the coagulation and the fibrinolytic and the inflammatory cascades.

DYNAMICS OF COAGULATION, FIBRINOLYSIS, AND COMPLEMENT ACTIVATION

The events depicted in Fig. 1 show that the delicate balance of clot formation and its lysis is maintained to achieve three main goals. First, blood is kept in the fluid state for adequate oxygen delivery to the tissues. Second, blood loss is minimised by formation of a clot

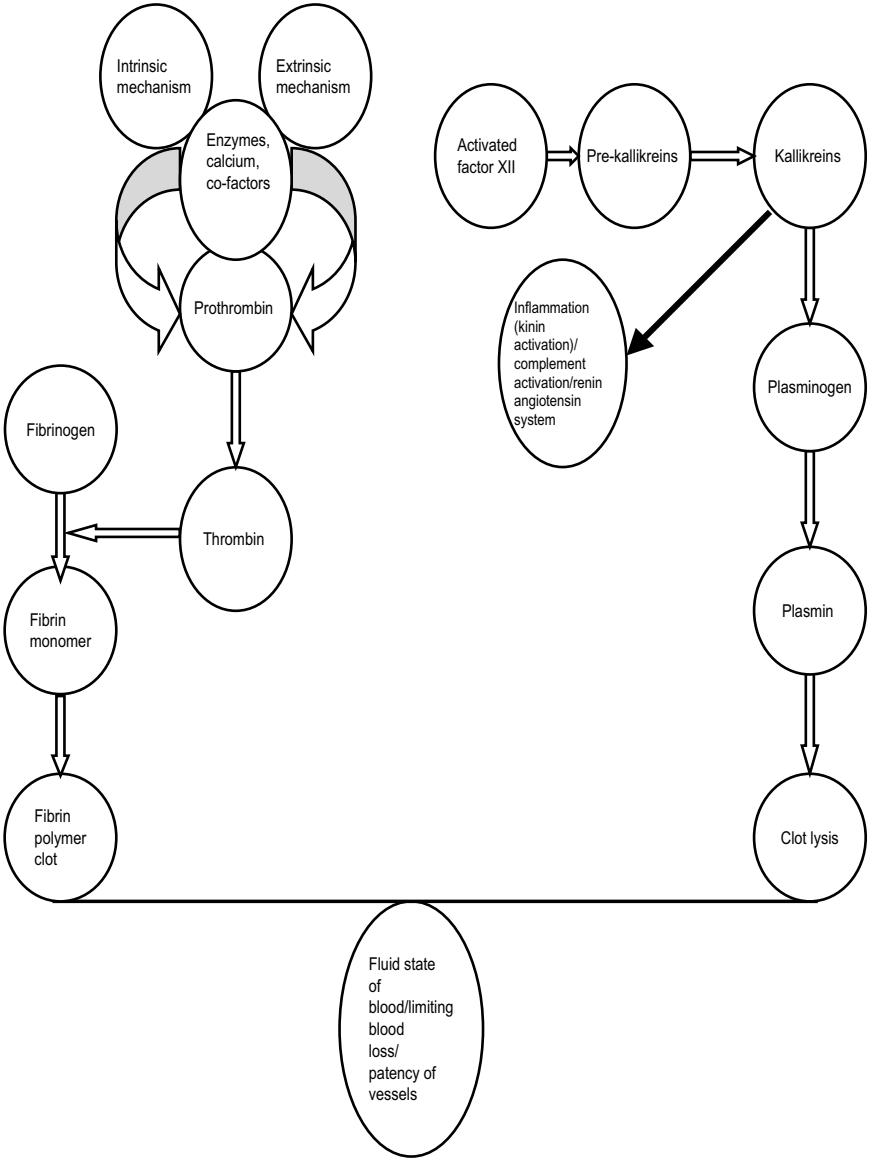

Fig. 1 Dynamics of coagulation, fibrinolysis and complement activation.

whenever there is injury to the vessel. Third, clots are lysed after the injury is repaired and the vessel patency is restored.

It is important to understand that the coagulation cascade can be triggered either by intrinsic or extrinsic stimulus. There is a sequential and an overlapping activation of the proenzymes in the presence of the co-factors and the substrates and with the appropriate pH and the temperature of the *milieu*. At all stages of this cascade, activated enzyme acts as a negative feedback mechanism and forms the rate limiting step.

Prothrombin is converted into thrombin that, in turn, converts fibrinogen into fibrin monomer. These fibrin strands are very weak and can be easily broken down. They are polymerised in the presence of factor XIII or fibrin stabilising factor, to form a strong framework or the skeleton of the clot. Platelets act as a local messenger of the stimulus of injury. They are activated at the site, releasing their granule contents (ADP, serotinin, histamine) with further propagation of the process and strengthening of the clot. This clot may later be lysed or may get organised with infiltration of fibroblasts, depending on the local need of the circulation.

Table 1. Factors Affecting Haemostasis

Preoperative	**Intraoperative**	**Postoperative**
Emergency operations	Prolonged CPB	Hypothermia
Thrombolised patients	Frail tissues (poor protoplasm)	Acidosis
Re-do surgery	Deep hypothermic circulatory arrest (DHCA)	Anaemia
Complex surgery	Calcification	Heparin rebound (inadequate protamine)
Congenital cyanotic heart surgery	Local infection with abscess formation	Hypertension
Renal failure		Excessive agitation of the patient with muscle contractility
Hepatic failure		Coagulopathy/ Thrombocytopenia/ Thromboasthenia
Diabetis mellitus		
Endocarditis/sepsis		
Old age		
Bleeding diathesis/vitamin deficiency		
Collagen diseases e.g. Marfan's disease		
Drugs: aspirin, heparin, warfarin		

The intrinsic coagulation pathway is initiated when blood comes into contact with a foreign surface and the factor XII (Hageman factor) is converted into its active form.[8,9] Activated factor XII triggers conversion of prekallikrein to kallikrein in the presence of high molecular weight kininogen (HMWK). This, in turn, acts on many pathways including conversion of HMWK to bradykinin, activation of prorenin to renin, complement activation, and conversion of plasminogen to plasmin, which in turn further activates complement and lyses the clot.

Factors affecting haemostasis preoperatively, intraoperatively and postoperatively can be found in Table 1.

CARDIOPULMONARY BYPASS (CPB)

In simple terms, CPB is a process in which blood is diverted from the heart and the lungs into the heart-lung machine, therefore, making it possible to operate on a still and bloodless heart. The heart-lung machine (Fig. 2) adds oxygen to the blood, removes carbon dioxide, and controls the temperature of the blood. It is also possible to add agents like buffers to the blood for pH control. CPB is a mandatory aspect of cardiac surgery in most of the adult and the paediatric cases. This technique has been used extensively in cardiac surgery for the last 50 years, since its first clinical use by John Gibbon in 1953.

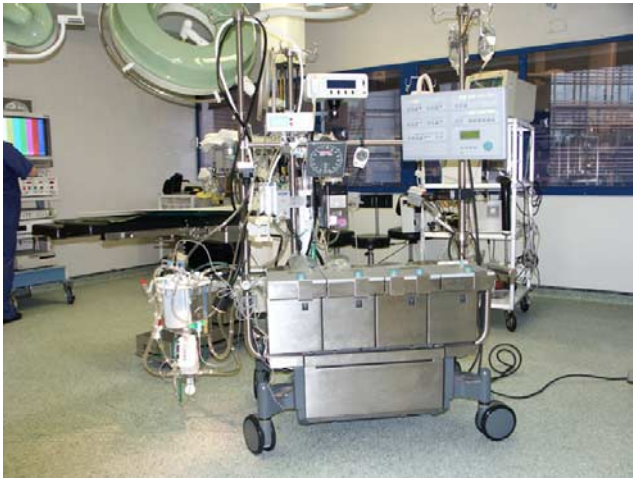

Fig. 2 Cardiopulmonary bypass machine.

Role of Oxygenators in Haemostasis

The last 50 years have seen major changes in the materials used and in the technology of the individual components of the heart-lung machine. As all these components are foreign to the host tissues they elicit strong inflammatory response leading to the activation of platelets, leucocytes, and the complement system and haemolysis. Oxygenators used in the early 1950s were either of rotating disc or of stationary screen types. They were large and cumbersome units and were not available in disposable form. They also gave rise to haemolysis, platelets' and leucocytes' activation, and large scale inflammatory response. In the 1960s and 1970s, bubble oxygenators were in widespread use. They worked on the principle of gas exchange taking place across the walls of microbubbles. The size of the individual bubble would determine the amount of diffusion of gases across the gas-blood interface. Bubble oxygenators required a pump downstream in the circuit, posing a potential hazard of major air embolism. In the 1980s and onwards, most of the cardiac centres transferred to the next generation of oxygenators called membrane oxygenators (Fig. 3). In these oxygenators, the gas exchange takes place across a membrane made up of either semi-permeable Teflon or silicone rubber. Membrane oxygenators come in either spiral coil form or in hollow fibre membrane form. A pump is used upstream in the circuit of the membrane oxygenator and, therefore, the risk of major air embolism is significantly reduced. These newer oxygenators are "kinder" to the blood and its formed elements. Therefore, they significantly reduce haemolysis, platelets' and leucocytes' activation, and complement system. This reduces the overall inflammatory response of the CPB. The use of filters, heparin coated circuits, and centrifugal pumps has further reduced the inflammatory response of the CPB.

ANTI-COAGULATION DURING CARDIOPULMONARY BYPASS

Heparin

Heparin is a naturally occurring polysaccharide secreted by basophils and mast cells, primarily in lung and liver tissues. The main role

Fig. 3 Modern membrane oxygenator.

of heparin is to prevent coagulation of blood in these slow flowing circulatory systems. Its molecular weight varies between 6000 and 22,000 Daltons depending on its source. Bovine lung heparins are thought to be more immunologically active than the porcine gut heparins. Heparin has a negatively charged molecule that is neutralised electrostatically by a positively charged protamine. The main advantage of heparin is that it can be infused parenterally in a more predictable fashion with its monitoring by the activated clotting time (ACT) on cardiopulmonary bypass and/or by activated partial thromboplastin time (APTT). It is quick in its onset of action and has a short half-life of around 4 to 6 hours. Heparin accentuates the action of anti-thrombin III by 10 s–100 s times. Anti-thrombin III mainly prevents conversion of prothrombin to thrombin. Heparin also acts on other steps of the coagulation cascade by inhibiting factors IX, X, XI, and XII.[10,11] As heparin does not have a fibrinolytic action it does not act on the thrombus that is already formed in the circulation. It merely prevents the further propagation of clot.

One of the major, but uncommon side effects of heparin is heparin induced thrombocytopaenia (HIT). The platelet count can fall to below 100,000/ml in those who are on heparin treatment. Counts less than 20,000/ml have, however, been reported rarely with this condition, in which life-threatening bleeding can ensue. In this situation, heparin infusions should be stopped immediately and the blood collected for the analysis of heparin antibodies. If they are not found, then platelet transfusion can be given safely without the risk of thrombosis. If further anti-coagulation is required, as in patients who are on haemofiltration, then heparin should be replaced with an iloprost (prostacyclin) infusion, a powerful platelet inhibitory prostaglandin. This agent should not be used as the sole anti-coagulant in CPB as it can give rise to thrombosis in the extracorporeal circulation. Other heparin substitutes can also be used in cases where heparin cannot be used. Herudin, danaparoid, argatroban, and LMWH are examples. Cardiac surgery using these substitutes is, however, still in its infancy. LMWH is mainly used only in the areas of prophylaxis of DVT and in the management of unstable angina. Its main advantage is that it is less immunogenic and less likely to cause thrombocytopenia. Its pharmacokinetics are more predictable, and there is no need to monitor APTT levels. It also can be given subcutaneously once or twice daily instead of the continuous infusion required in the case of unfractionated heparins.

Allergic reaction to heparin is rare, however, a condition called heparin resistance may develop in patients who have prior heparin exposure. The mechanism of this condition involves depletion of anti-thrombin III, leading to the failure of inhibition of formation of thrombin. The treatment of this condition paradoxically involves giving FFP transfusions to replenish the anti-thrombin III levels.

The phenomenon of heparin rebound is widely incriminated for postoperative bleeding. Various theories have been put forward for this phenomenon. The initial dose of protamine given for reversal may be inadequate, or it may be that heparin is released into the circulation from early break down of heparin-protamine complexes or from other tissue depots. It also may be due to the fact that protamine has a shorter half-life than that of heparin. Whatever the

theory, it is a very difficult phenomenon to prove objectively in a clinical setting. In practice, a small additional dose of protamine may be given postoperatively in patients who are bleeding and have abnormal APTT, without causing any harmful effects.

The batch potency of heparin differs on the basis of its source, and patient sensitivity and metabolism vary between patients.[12] Heparin monitoring is, therefore, strongly recommended in cardiopulmonary bypass. ACT is one of the methods used during cardiac surgery.[13,14] The clotting time, which is prolonged due to heparin for up to 70 to 80 minutes, is measured by the process of activation with the use of diatomaceous earth. With celite-ACT it is recommended to be > 750 seconds and with kaolin-ACT it is recommended to be > 450 seconds in CPB. One milligram of heparin may contain potency of 80 to 130 IU. Therefore, after the initial dose of 300 U/kg, ACT is measured, and if it is > 300 seconds then cannulation can be done and the pump suckers can be switched on. With an ACT > 400 seconds CPB can be established, otherwise an extra dose of heparin is given.[15] The ACT is measured every 30 minutes and is kept around 450 seconds. The level of 400 seconds is widely accepted, and research by J. J. Verska[16] has shown that at these levels, the microcirculation is free of thrombosis. The ACT is a less accurate measure in hypothermic patients and in cases where more than 5 mg/kg of heparin is required. Despite these drawbacks, currently available systems like Haemocron are widely used due to their user friendliness and compactness. Newer systems use the principle of direct assay of heparin activity. They are complex to use, but they overcome the drawbacks of the Haemocron as they are accurate both in the setting of hypothermia and with high heparin doses. Heparin requirements during paediatric cardiac surgery are more or less the same as in adults, except during cases of deep hypothermic circulatory arrest where the doses required are higher than those in normothermia.[17] Hypothermia is thought to derange coagulation due to a decrease in enzymatic activity and in collagen induced platelet aggregation. Hypothermia also gives rise to a marked increase in fibrinolysis, thrombocytopenia, and hepatic dysfunction that further add to the causes of bleeding.

At the end of cardiopulmonary bypass each 100 U of heparin is neutralised with 1 mg of protamine. On suspicion of heparin

rebound, additional small doses of protamine may be given in intensive care unit. Protamine is thought to have anti-coagulant action only in large doses. This action is seen rarely in clinical practice.

Protamine

Protamine sulphate is a simple protein and is a strong base in characteristics, as against heparin which is acid. Therefore, it forms electrostatic complexes with the molecules of heparin and neutralises its action by inhibition of anti-thrombin III. It acts on all stages of the coagulation cascade. Protamine is extracted from a fish sperm and can show cross-immunity by giving a hypersensitivity reaction in patients who are allergic to fish protein. Protamine can also, by the same mechanism, give rise to allergic reactions in those who have a history of testicular trauma or procedures like vasectomy, in which there is a breach in the blood-sperm barrier. Patients, who are on protamine containing insulin preparations (PZI, NPH insulin), can also elicit strong reactions to protamine. Apart from minor reactions like skin rash, nausea, and lassitude it can give rise to some major reactions like hypotension, hypertension, bradycardia, and severe bronchospasm. Urticaria with severe angioedema and pulmonary hypertensive crises with right heart failure are other major reactions. The mechanism of this is thought to be due to the release of the contents of pulmonary mast cell granules, particularly histamine. To avoid this potential complication, some surgeons give protamine directly into the left atrium or into the aorta. Only in large doses can protamine give rise to severe bleeding. Therefore, protamine is given as a slow intravenous injection, at the rate of not more than 100 mg over 3 to 5 minutes. Protamine reactions should be treated with steroids and anti-histaminics, and the general management of cardiac failure should be done with inotropes and optimal fluid infusion.

Role of Platelets in CPB and Anti-platelet Agents

In CPB, platelets decrease in numbers partially due to haemodilution.[18] They are also activated with the modification of membrane receptors. ADP induced platelet aggregation is markedly

Table 2. Drugs Giving Rise to Thrombocytopenia

Penicillins/Cephalosporins
Diuretics/ACE inhibitors
Unfractionated heparins
Anti-metabolites/Alkylating agents

Table 3. Drugs Giving Rise to Thrombosthenia

Aspirin/Dipyridamol/Clopidogrel
Indomethacin/Other NSAIDs
Alcohol
Oestrogens
Diuretics
Ranitidine

impaired from the onset of CPB and is eventually restored around five days postoperatively.[19] Platelet factor IV, thrombospondin, and β-thromboglobulin are released from $\propto$-granules.[20,21] Thromoxane A2, which is a strong vasoconstrictor in the circulation, is also released.[22]

Various drugs can give rise to derangement of either platelet numbers or their function. The list is long, but some commonly used drugs are shown in Tables 2 and 3.

Platelet function can be objectively measured and evaluated by various methods. One of the simplest is the bleeding time measurement. Other methods include aggregometry with ADP, adrenaline and arachidonic acid, monoclonal antibody measurement, flow cytometry, and electron microscopic measurement of platelet granule contents.

Thromboelastograph (TEG)

This was originally described in 1948 by Professor Hartert in Germany. Till the 1980s its use was somewhat limited, but when liver transplantation became a worldwide phenomenon, its use greatly increased. Since then it has been used in diverse groups of clinical settings, such as, cardiac surgery, obstetrics, vascular surgery, and trauma. As

against the conventional tests for blood coagulation, which look at the isolated stages of the coagulation, the thromboelastograph looks at the whole process of coagulation. The measurement is displayed as a graph from the clot formation to fibrinolysis. It also measures the kinetics of clot formation and the tensile strength of the clot by monitoring platelet function, fibrinogenesis, and vaso-elastic assessment of thrombin formation. Abnormal TEG profiles seen in the perioperative period may predict postoperative bleeding. Some studies have, however, failed to prove the usefulness of TEG in predicting postoperative bleeding.[23] New versions of TEG have the ability to assess the effects of aspirin and clopidogrel. This may change the cardiac surgical usage of these machines. A normal TEG suggests that the postoperative bleeding is not caused by a coagulation factor deficiency, deranged platelet counts or function, or fibrinolysis. Many centres in the US run the TEG in an operating room satellite lab, and the TEG curve output is transmitted to the operating room, enabling everyone concerned to view it. TEG is the most useful indicator of excessive fibrinolysis, occurring due to the excessive production of tissue plasminogen activator (t-PA) from the vascular endothelium or the lack of its clearance. D-dimer is not a good surrogate for measuring fibrinolysis; it measures intravascular fibrin and not its lysis.

Management of Postoperative Bleeding

Understanding the mechanisms of coagulation/fibrinolysis and the role of platelets in CPB is essential in managing the postoperative bleeding following cardiac surgery. The management of postoperative bleeding starts in the preoperative period, with full optimisation of the patient. All medications that give rise to excessive bleeding should be discontinued in the preoperative period, if the clinical circumstances permit. In cases of tight left main disease, unstable angina, or critical coronary narrowings it may be deemed safer to balance the risk of bleeding against the risk of preoperative thrombosis. When there is clinical urgency, patients may still be taking medications including anti-platelet agents, warfarin, and LMWH,

and there may not be an opportunity to stop them. Patients who have recently had thrombolytic therapy may also need intervention. In these scenarios one has to anticipate the possibility of postoperative bleeding and arrange for the blood products. One may consider the use of anti-fibrinolytic agents like aprotinin or tranexamic acid, intraoperatively. This strategy may also be followed in re-do operations, complex operations, and paediatric cases. In addition, patients with sepsis, renal impairment, or DM and elderly patients can benefit from such intervention.

Intravenous infusions of heparin should be discontinued 4 to 6 hours prior to the operation. Warfarin should be discontinued at least 48 to 72 hours before the planned operation, and the anti-platelet agents (aspirin, clopidogrel) that block platelets irreversibly by acetylation of platelet cyclo-oxygenase (thromboxane A2 induced aggregation is inhibited for the life of platelets), should be discontinued at least seven days prior to a planned operation. This provides adequate time for a new set of platelets to be released into the circulation.

Vitamin K

Vitamin K is a fat-soluble vitamin that is generated in the gut by the bacterial flora. It is also present in the normal diet (in dark green vegetables like spinach and broccoli and in oils, particularly soyabean oil). It is absorbed with the help of bile salts in the liver to form clotting factors II, VII, IX, and X and proteins C, S, Z, and M. Activated protein C functions as an anti-coagulant by degrading the activated forms of factors V and VIII. Protein S is the co-factor for the activation of protein C. Neonates, where the gut flora is not yet developed and patients suffering from malnutrition or hepatic dysfunction are prone to vitamin K deficiency. Neonates can be given 1 mg of vitamin K before the operation. Adult patients falling in the above-mentioned category should receive 1 to 10 mg of vitamin K. The action of warfarin is reversed with the transfusion of fresh frozen plasma in the acute setting and with vitamin K in the elective setting if the prothrombin time persists above the normal level, despite stopping warfarin for 48 to 72 hours.

Sickle Cell Disease and Thalassemia in Cardiac Surgery

Sickle cell haemoglobinopathy

The Hb-S gene may manifest in either homozygous form causing sickle cell disease or in the heterozygous form known as sickle cell trait. This type of haemoglobinopathy is prevalent in 8% of American Blacks and 20 to 50% of African Blacks. In sickle cell trait 38 to 45% of Hb-A is replaced by Hb-S, while in sickle cell disease 75 to 95% of haemoglobin is Hb-S. With different stimuli, Hb-S changes its conformation leading to sickling of the red cell. This sickled cell gives rise to thrombosis in peripheral tissues. Important stimuli precipitating sickling are hypoxia, dehydration, infection, and hypothermia. Patients with sickle cell disease are prone to different types of crises including aplastic, vasospastic, and thrombotic depending upon its pathogenesis. The diagnosis of this condition is made by screening the high-risk ethnic population by sickle test and by a haemoglobin solubility test. It can be confirmed by electrophoretic analysis. Sickle cell positive patients undergoing cardiac surgery pose a particular challenge to the anaesthetists due to the possibility of triggering sickle cell crises during CPB. In these patients, fluid balance is carefully managed to avoid the dehydration of peripheral tissues. Prevention of hypoxia is also vital. During cardiac surgery most patients are cooled below 37°C and, therefore, utmost care is taken to keep the patients well-oxygenated. Infections are controlled with appropriate antibiotics.

Thalassaemias

Thalassaemias are a heterogeneous group of disorders. They have a genetically determined reduction in the rate of synthesis of one or more types of normal haemoglobin polypeptide chains. Thalassaemias were originally described in the people of Mediterranean origin. It is now, however, known that they are distributed geographically through the Middle East, India, and South-east Asia. Depending on the lack of α or β chain production, they are named as α or β thalassaemias, respectively. They can be in a major or a minor form depending on the manifestation of the gene. The diagnosis is based on the electrophoresis or on the microcolumn chromatography. Patients

with thalassaemias present with anaemia that requires repeated blood transfusions, massive hepato-splenomegaly, and hyperplastic bone marrow changes in the skull and in the other long bones. The patients are prone to congestive cardiac failure, cirrhosis, and diabetes mellitus due to haemosiderosis. The mortality of the major forms of thalassaemias is high, and patients do not often survive beyond the third decade of life. Patients with thalassaemias undergoing cardiac surgery are, therefore, likely to be in their first or second decade of life. For these patients, the focus of attention is on the management of their anaemia, infection, and other systemic problems seen in thalassaemias.

Intraoperatively, meticulous attention and maintaining respect for the tissues are cornerstones in any blood conservation programme. We have moved long away from the days when the surgeon had only mosquito clips and ligatures for attaining haemostasis. Today, surgeons have a wide choice of topical agents, drugs, and allograft and homograft tissues that can be used for good haemostasis. Ligaclips, bipolar diathermy, stapling devices, and artificial materials (for buttressing frail tissues) have all made a significant contribution along with major advances in the manufacturing technologies of needles, suture materials, and other equipment.

Materials like Teflon can be used as pledgets or as a strip to reinforce the delicate and frail tissues (in old age, aortic dissection) and the areas with excessive calcification. Natural tissues are thought to be better in resisting infection in cases of root abscesses. Pericardial autografts or allografts and homograft or autograft valves (Ross procedure) are used widely to limit infection and bleeding. Goretex (expanded PTFE) is thought to be better in limiting the bleeding from the needle holes, as it swells when it comes into contact with blood. Sutures made of Goretex are also available.

Skilled management of the heart-lung machine helps to minimise blood injury, haemolysis, and fibrinolysis. The use of membrane oxygenators, haemofilters in the circuit, cell savers, micro filters, centrifugal pumps, and thromboresistant materials are examples of the advances in perfusion technology. There is still controversy over the use of inline arterial filters. By avoiding large pressure gradients

in the circuits, cooling and rewarming the patient without large gradients, and using pump suckers without churning of the air and blood mixture perfusionists and surgeons can reduce postoperative bleeding. Anaesthetists obviously play a significant part in maintaining optimal haemodynamics throughout the operation by avoiding extremes of the blood pressure.

One author, B. G., was taught many years ago as a registrar at the National Heart Hospital to remember the seven Ps of bleeding. They are *pressure* (*BP control*), *prolene* (*surgical haemostasis*), *platelets*, *plasma* (*FFP*), *protamine*, *PEEP* (*to achieve controlled tamponade*), *and prayer* (as mentioned in Table 4). This aide-memoire can be a useful method for thinking through the various factors that may be contributing to a bleeding situation and provide a pointer to management. This simple checklist can act as a good bedside aide-memoire to ensure all reasonable measures are considered.

Topical Agents

Agents like Surgicel (cellulose) and Gelfoam (gelatine foam) have been in use in surgical practice for many decades. Tisseel contains two separate injections of fibrinogen and thrombin that rapidly form fibrin clot locally at the required site. As it contains biological materials, there is a potential risk of transmission of hepatitis B antigen. Areas like bleeding needle holes can be sprayed with this agent when the field is dry. Gelatin/Resorcinol/Formalin (GRF), also known as bioglue, has shown good results in friable tissues and in cases of aortic dissection.[24]

Table 4. An Aide-Memoire for Bleeding

Pressure
Prolene
Platelets
Plasma
Protamine
PEEP
Prayer

On transfer of the patient to the intensive therapy unit, optimal control of its haemodynamics can be enhanced by appropriate sedation. Emphasis is placed on avoiding the swings of hypotension and hypertension that can exacerbate postoperative bleeding. A few centres follow a strategy of extubating the patients on the operating table immediately after the cardiac operation. In those centres, surgeons and anaesthetists make decisions in accordance with local protocols. It is a common practice to keep patients who have had long times in CPB, DHCA, or other complex procedures, sedated for a short time until it is clear that the patient is stable from all points of view. Excessive agitation leads to excessive muscle activity of the patient that can increase the blood loss from the raw areas of the operative field. All patients should be actively rewarmed with the help of a warming blanket to avoid the consequences of deranged clotting in hypothermia. A low haemotocrit itself is a factor in the propagation of the cycle of bleeding, and patients with low haemoglobin should be transfused to maintain the haemoglobin at around 8.5 g/dl. The presence of an acidosis can cause derangement of clotting enzymes and its serious action on the heart, leading to a state of low cardiac contractility. Treatment depends on identifying the cause. Haemodynamics should be optimised to improve the peripheral tissue circulation. A diuresis can be achieved by optimal filling and by drugs like frusemide and mannitol. Renal function can be supported by haemofiltration of the patient. The blood sugar can be maintained within a tight range to avoid the possibility of acid production by anaerobic metabolism, which may occur in ischaemic areas of the body. Acidosis can also be treated with an infusion of 8.4% $NaHCO_3$.

On arrival of the patient in the ITU, a clotting screen is sent. If the ACT is above the normal level of 120 seconds, then a small dose of protamine (50 mg over 2 to 3 minutes i.v.) can be given if the patient has excessive postoperative bleeding. A platelet transfusion should be considered in those who are bleeding with low platelet count ($< 40{,}000$/cu mm) or with abnormal TEG profile as discussed earlier. A single bag of platelets is created by pooling from the multiple donors. Therefore, there is an increased risk of transmission of CJD and hepatitis B/C. Blood banks, do all they can to minimise these risks, from testing programmes to donor selection.

A prolonged INR can be corrected with transfusion of FFPs. Excessive fibrinolytic activity can be demonstrated with low levels of fibrinogen and high levels of fibrin degradation products (FDPs). Cryoprecipitates and anti-fibrinolytic drugs like aprotinin and tranexamic acid may be useful adjuncts in this situation.

Anti-fibrinolytic Agents

Aprotinin

This drug has been in clinical use for the past three to four decades. It is a serine protease inhibitor that is extracted from bovine lung tissue. It has a number of biochemical effects on the coagulation system and, therefore, is likely to have several mechanisms of action. Aprotinin in high dose regimen is known to inhibit kallikrein and plasmin.[25] Recent studies suggest that the most striking differences between aprotinin treated and untreated patients exist in the fibrinolytic systems. There is a reduction in the formation of FDPs,[26] increased α2-anti-plasmine,[27] and plasminogen activator inhibitory activities and decreased t-PA release from endothelial cells[28] in treated patients. High dose aprotinin prevents the prolongation of the bleeding time seen after CPB, suggesting that the platelet function is preserved with this agent.[29] The correlation between the intrinsic coagulation system and the complement system is reflected by the inhibitory effects of aprotinin on kallikrein, the common link between these systems. Complement amplification may be initiated by thrombin and plasmin, therefore, inhibition of the intrinsic pathway of coagulation as well as direct inhibition of plasmin by aprotinin would be expected to inhibit this process.[30]

Aprotinin (Trasylol) is given as a test dose of 1 ml before the loading dose is given. The preparations used prior to its use in cardiac surgery contained alcohol as a preservative, but the preparations made in Germany are free of any preservatives. Therefore, they can be given in higher doses without any toxicity issue. Hypersensitivity reactions are known and are more common in patients who have prior exposure to aprotinin (5% incidence in re-exposure within 6 months, 0.9% incidence in re-exposure after 6 months).[31] Anaphylaxis is known to occur sometimes even after negative test dose

response, therefore, pump-prime is given 20 minutes after the full loading dose has gone in. A loading dose is given before the sternotomy is performed. Two regimens commonly used are shown in Table 5. A range of operations are likely to benefit from aprotonin. These include re-do operations and operations for endocarditis and those with complex repairs. Patients, in whom a long bypass is anticipated, may also be benefited. A few studies[32] have shown reduction in the blood loss and in the requirement for blood transfusions in paediatric cardiac surgery. The mix of patients in these studies was, however, heterogeneous. Therefore, it is difficult to draw any firm conclusions. Although aprotinin has demonstrated some clinical efficacy in a few trials of paediatric surgery, more studies are needed to firmly recommend aprotinin in this setting. Aprotonin is not indicated in the first time CABG patients that are otherwise low risk cases for postoperative bleeding. The prothrombotic effects of aprotinin may give rise to the graft blockages. Studies conducted in the early 1990s have, however, tried to refute such claims.[33] Renal impairment and hypersensitivity to the drug are other contra-indications.

During CPB if aprotinin is given, then Celite-based ACT is maintained at 750 seconds and Kaolin-based ACT is maintained at 480 seconds. During DHCA the ACT is maintained at 1000 seconds and, therefore, an additional dose of heparin is given just before stopping circulation in this situation.

Table 5. Regimen of Trasylol Use in Cardiac Surgery

High dose regimen	2 million units (200 ml) bolus i.v. over 30 minutes (after test dose of 1 ml) 2 million units in pump-prime	500,000 units/hr over 3 to 4 hours i.v. post-op till bleeding < 100 ml/hr
Low dose regimen	1 million (100 ml) units bolus over 30 minutes (after test dose of 1 ml) 1 million units in pump-prime	250,000 units/hr over 3 to 4 hours i.v. post-op till bleeding < 100 ml/hr

Other anti-fibrinolytic agents like Tranexamic acid, EACA, and desmopressin (DDAVP) are also used in clinical practice of cardiac surgery. Tranexamic acid (Cyklocapron) is used more regularly due to its milder toxicity. Before the sternotomy 2 g is given, and 1 to 2 g may be given after cardiac surgery if the patient continues to bleed. It can be given along with Aprotinin.

ROLE OF RE-EXPLORATION

Following cardiac surgery a few patients continue to bleed in the intensive care unit, and despite all the measures mentioned in the previous section being undertaken, around 3 to 5% of those need to be re-explored. The indications, timing, and methods of re-exploration vary from centre to centre, but there are some basic guidelines which govern this situation.

In a 75 kg person with a normal coagulation profile, more than a litre of bleeding in the first 2 to 3 hours or more than 150 ml in each hour for 5 to 6 hours may be an indication for re-exploration. Some patients show apparent stability for the first 8 to 12 hours with acceptable levels of bleeding and then they start bleeding. In this situation, more than 200 ml for a consecutive 3 to 4 hours with normal coagulation should warn the surgeon about the possibility of a surgical cause for the bleeding. After the first postoperative day, any bleeding that is more than 300 ml and associated with a drop in the haematocrit or a change in the haemodynamics, is of concern.

Clearly, in a 40 kg person 700 ml of bleeding is as significant as one litre in a 75 kg person. Similarly, in a 120 kg person the limit for indication of exploration may be extended to 1500 to 1800 ml. All decisions in these situations should be based on the overall condition of the patient. In the paediatric group, more than 5 ml/kg/hr for 2 to 3 hours consecutively or more than 3 ml/kg/hr for 5 to 6 hours should be considered as significant bleeding.

Rarely, bleeding can be concealed and the suspicion of bleeding can only be gauged by the haemodynamic instability or by the unexplained drop in the haematocrit with persistent need for transfusion. In this scenario, if time permits, a chest radiograph and an

echocardiogram are of an immense value, as a large collection of blood in either mediastinum or in the pleural space would demand re-exploration. A sudden decrease in the recorded blood loss from the drains should alert the surgeon to the possibility of blocked drains rather than an actual decrease in the amount of bleeding. In these cases, the surgeon should rule out that possibility by thorough milking of the drains and by dislodging of the clots from the drains.

When surgery has been fraught, and it has been noted that the tissues are friable, the surgeon may choose to accept higher than normal blood losses. In this situation, extra-clinical vigilance is mandatory.

Cardiac Tamponade

If the amount of bleeding exceeds the capacity of the drainage tubes, then it will accumulate in the pleural space and the mediastinum and may lead to cardiac tamponade. In this scenario, ever expanding blood clot can progressively compress the heart chambers, especially the atria. The surrounding bony cage being rigid, leads to a rapid decrease in the venous return and the cardiac filling, both causing a low cardiac output state. Keeping both pleurae open does not offer immunity against cardiac tamponade, as commonly thought, but putting more mediastinal drains may delay the onset of this situation.

Cardiac tamponade may manifest itself with hypotension, high jugular pressure, and poor end-organ perfusion resulting in oliguria. The patient may be peripherally cold and clammy, and the hypotension responds poorly or temporarily to inotropes like calcium chloride, given intravenously. In the paediatric setting, the first sign of tamponade may be failure to rewarm in a normal way. Many cardiac centres follow the doctrine “if in doubt, re-explore”.

The Role of Wound Packing

As the surgical expertise and the management of haematological deficits have improved, the frequency of requirement for wound packing has decreased. Wound packing, however, remains a very useful method of salvaging a patient in a seemingly dire situation.

Topical haemostatic agents like Tisseel and floSeal can be applied to a specific raw area of the surgical site, followed by a light packing with Surgicel. The remaining area of the wound can be packed with swabs soaked in warm saline. The drains are inserted and, then, the wound can be closed with the temporary sutures. If stable haemodynamics can be achieved, the patient can be transferred to the ITU with a view to returning to the operating theatre in 24 to 48 hours.

During these 24 to 48 hours, the patient is kept in optimal haemodynamic state, with strict avoidance of hypertensive episodes. The patient's coagulation profile and other abnormal parameters like acidosis, hypothermia, and anaemia are corrected.

Haemostasis is often successful with this manoeuvre, but potential infection of the mediastinum remains a major concern. Mediastinitis and sternal infection following chest packing is as high as 14%[34] and carries a high mortality.

Causes of infection in these cases are multi-factorial and as follows:

- Contamination.
- Presence of foreign body.
- Immunocompromise due to CPB/multiple blood transfusions.
- Low cardiac output state.
- Multi-organ failure (MOF).

Auto-transfusion, Cell-Savers, and Haemodilution in Cardiac Surgery

Despite the best efforts of the transfusion service, receiving homologous blood confers potential risks on the patient. This together with the rising cost of blood products has increased the practice of autotransfusion. This can be achieved by two methods. In the first method, the patient donates a unit of blood every week for 2 to 3 weeks before the elective operation, and the donated blood can be transfused back to the patient during the perioperative period. A major disadvantage of this method is that the stored blood is devoid of many clotting products and platelets. In the second method, the blood is collected during the operation, after anaesthesia, but before heparin has been administered. Up to two units of blood can be collected with this technique over a short period of time and replaced with a similar

volume of colloid or crystalloid expanders. The collected blood can be transfused back to the patient at the end of the operation, when surgical haemostasis has been largely achieved. The blood is fresh in this method of auto-transfusion, and haemodilution is also achieved. There is, however, a possibility of haemodynamic instability in critically ill patients.

Cell-savers (as shown in Fig. 4) are being increasingly used in cardiac surgery, in many centres. With the cell-saver, blood that is shed during the surgery is collected with the addition of heparinised saline, to prevent clots in the circuit. The collected blood is washed and filtered, and the red cells are suspended in normal saline, ready for transfusion back to the patient. This red cell mass is free of heparin. Cell-savers can be connected directly to the chest drains that collect postoperatively shed blood. This shed blood can then be recovered, washed, and returned. This latter method can reduce the need for re-exploration of the patient, although it is rarely successful when the bleeding is brisk.

Fig. 4 Cell-saver used routinely in cardiac surgery.

Haemodilution is another method of reducing blood loss. During CPB, the haematocrit is maintained at around 25 to 30 instead of the normal 45 to 50. This technique reduces the viscosity of blood and, therefore, improves the rheological function of the formed elements of the blood. With haemodilution there is also improved microcirculation of the tissues, which is a by-product of the decrease in viscosity. The third and the most important potential benefit of haemodilution is that it decreases the amount of injury to the blood and the level of inflammatory response.

SPECIFIC CHALLENGES IN CARDIAC SURGERY

Surgery in Jehovah's Witnesses

Patients who are Jehovah's Witnesses have certain religious requirements during cardiac surgery, although interpretation and practice varies. All these patients are likely to refuse transfusion of blood or blood products that are non-autologous. Some patients will accept autologous blood that has been stored. Other patients insist that all the blood to be transfused should remain in a circuit connected directly to them. Informed consent as to what is acceptable and what the risks are is of particular importance.

Patients can be started on iron supplements and recombinant erythropoetin injections before the operation, to increase the haematocrit. All medications that can increase perioperative bleeding should be withdrawn. During the operation, use of meticulous technique and attention towards haemostasis is vital. Anti-fibrinolytic medications like aprotinin and tranexamic acid can be used even before the sternotomy is performed.

The use of the cell-saver is important for these patients. A greater degree of haemodilution can be accepted to minimise blood injury and blood loss. Post-CPB heparin reversal is delayed until the surgical haemostasis has been confidently secured. At the end of the procedure, the haemofilter is used to remove the excessive volume of the fluid. The remaining red cell mass can be transfused while still in the circulation. Postoperatively, low haemoglobin is often accepted, and after the patient has started enteral feeds, iron and erythropoetin

injections can be resumed. In a situation where the surgeon will be operating on a child whose parents are Jehovah's Witnesses and the child cannot yet sign his/her own consent for operation, the parents' wishes are carefully noted. It is of interest to note the attitude of different legislatures around the world, when surgeons have disregarded the wishes of the parents. These decisions are best made preoperatively, and surgeons undertaking such work should understand their local situation.

EMERGING TECHNOLOGIES

Future developments in cardiac surgery need to focus mainly on four areas. First, it is necessary to develop the techniques of minimal access; second, to perform cardiac surgery without the need for CPB; and third, to reduce the need for heparin or to find its alternatives. There have been significant advances in the first area, and today cardiac surgery can be performed with smaller incisions (MIDCAB) or with the help of robots, as shown in Figs. 5 and 6 (ENDO ACAB, or complete robotic mitral valve repairs or coronary artery surgery).

Fig. 5 Robotic device for coronary artery surgery.

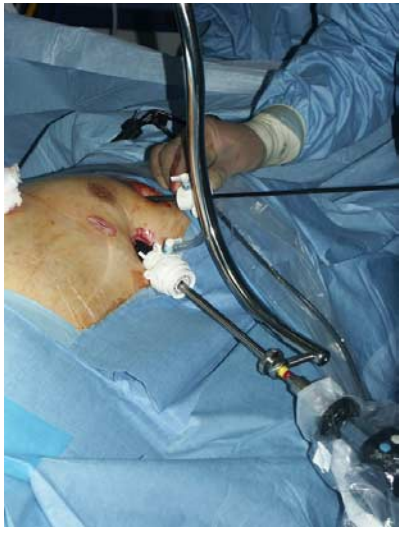

Fig. 6 Robotic coronary artery bypass surgery.

With smaller incisions there are less sources of potential bleeding. In addition, surgery is performed without the need for CPB (OPCAB), either through conventional incisions or through the smaller incisions. The major advantage of OPCAB is avoidance of the inflammatory response to the CPB and the blood injury that goes with it. Heartport is a method of going on CPB via femoral cannulations, with the help of specifically made cannulae. The surgery is performed through smaller incisions. The third area is to develop techniques where the need for heparin is reduced (heparin coated pump circuits) and to develop heparin substitutes that can be used in patients with heparin allergy or with HIT. This area is still under development and needs future research. The final area concerns the development and the use of fully artificial blood.

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Haemostasis in Liver Surgery

Madhava Pai, Ruben Canelo and Nagy Habib

HISTORY

The complex anatomy and multiple functions of the liver have afforded it proper respect from surgeons over the years. During 2000 to 3000 BC, the liver was used through animal sacrifices, in the art of divination and was considered the seat of the soul.[1,2] The Greeks continued this tradition and in the legend of Prometheus, illustrated the regenerative properties of the liver.[3]

Berta performed the first liver resection in 1716, by resecting a part of the liver that was protruding following trauma.[4] von Bruns, who operated on an injured soldier in the Franco-Prussian war, repeated the procedure only in 1870.[5] Langenbuch performed a left hepatectomy for a mess lesion and, therefore, carried out the first successful elective liver surgery in 1888.

In 1902, Pringle described the concept of vascular inflow occlusion by clamping the portal triad and controlling bleeding.[6] In 1903, for the first time, Anschutz described the finger fracture technique.[7] Wendel performed the first anatomical lobectomy for a right-sided

tumour in 1911.[8] By 1940, successful liver resections for matastatic colorectal cancer were being reported by Cattell.[9] Ligation of portal pedicle and hepatic vessels prior to hemihepatectomy was performed by Lortat-Jacob in 1952.[10] Total Hepatic Vascular Exclusion (TVE) was introduced by Heaney in 1966. This involved the occlusion of the portal structures, the infra and the supra-hepatic vena cava, and the supra-coeliac aorta prior to liver resection.[11] In the 1980s, Bismuth and Huguet modified Heaney's technique by omitting aortic clamping. This yielded acceptable mortality and morbidity figures, enabling more extensive use.[12–14]

The prevention of blood loss is one of the first priorities of the surgeon during hepatic resection. Blood transfusions have been linked to increased postoperative morbidity and mortality.[15–17] In addition, perioperative blood transfusion in cancer patients has been postulated to induce immunosuppression that adversely affects postoperative outcome and duration of cancer-free survival.[18–20]

In the past few decades, surgical techniques to facilitate haemostasis have been developed, and they have improved the outcomes of liver resection. The techniques include monopolar and bipolar diathermy, infrared coagulation,[21] argon beam coagulation,[22] CUSA,[23,24] ultrasonic (harmonic) scalpel,[25] water jet cutter,[26,27] and

Table 1. Classification of Different Techniques of Haemostasis in Liver Surgery

Dissection Techniques
Finger fracture
Ultrasonic dissector
Water jet
Haemostatic Techniques
Infrared coagulation
Diathermy
Argon beam
Laser photocoagulation
RF assisted
Topical sealants
Combined Techniques
Ultrasonic (harmonic) scalpel
CUSA
Floating ball (tissue link)

radio frequency (RF) assisted resection.[28] These devices are welcome adjuncts to the basic techniques of finger fracture and electrocautery (Table 1).

ARGON BEAM COAGULATOR (ABC)

It is most useful in achieving final haemostasis of the cut liver surface, after discontinuation of vascular occlusion. ABC utilises a jet of inert non-flammable argon gas, instead of the air jet of standard electrocautery, to conduct radio frequency currents to the target tissue.[22] There is less hyperthermic injury compared with results obtained by electrocautery. The argon gas also clears blood from the site of dissection, enabling the formation of a more adherent, haemostatic eschar than in the case of electrocautery. Therefore, the resulting eschar is thinner, more adherent, and more uniformly distributed.[29]

LASER PHOTOCOAGULATION

There are CO_2 as well as Neodymium: yttrium aluminium-garnet (Nd: YAG) lasers. Lasers with contact tips are generally referred over free beam lasers. The lasers generate temperatures as high as 2001°C and can produce varying depths of coagulation depending on the type of tip used and the amount of hepatic blood flow at the time of surgery. A broader zone of coagulation, up to 7 to 8 mm, can be achieved by reducing the blood flow through vascular occlusion.[29] The main advantage of the laser is that dissection through a tough, cirrhotic liver is much easier and faster. One drawback, however, is that the surgeon cannot identify vessels and biliary structures prior to their division. Some groups have reported higher blood losses with laser, compared with argon beam and ultrasound dissection.[30]

ULTRASONIC DISSECTOR

Hodgson introduced ultrasonic dissector for liver surgery in 1984.[31] This is a hand-held instrument consisting of a titanium tip that oscillates at an ultrasonic frequency of 25,000 vibrations per second. When placed against tissue, fat and hepatocytes are destroyed by a

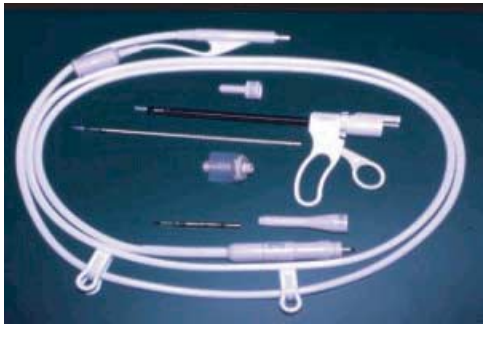
cavitational effect based on their higher water content. In contrast, vessels, ducts, and nerves, which contain fibrous tissue with more collagen and less water content, are left relatively undamaged.[32] The instrument also has an irrigation port to cool the tip and a suction port to aspirate the irrigant and fragmented tissue. In performing the dissection of liver tissue, the fibrous capsule of the liver requires division by electrocautery as the ultrasonic dissector is not efficient in dividing these tissues. After the parenchyma is exposed, the ultrasonic dissector is employed to destroy the parenchymal tissues and leave vessels and ducts to be electively divided. For small vessels and ducts, electrocautery is sufficient. For larger vessels and ducts, ligation using ties or clips should be employed. The use of the ultrasonic dissector has had a significant impact on patient morbidity and mortality, dramatically reducing blood loss, especially when used in conjunction with intra-operative ultrasound (IOUS).[33] A new offshoot of the ultrasonic dissector is the ultrasonically activated coagulating (*harmonic*) scalpel, which is described below.

ULTRASONICALLY ACTIVATED COAGULATING SCALPEL AND SHEARS

The ultrasonically activated coagulating scalpel cuts and coagulates by using lower temperatures than those used by electrosurgery or lasers. This technology controls bleeding by coaptive coagulation at low temperatures ranging from 50 to 100°C. Vessels are coapted (tamponaded) and sealed by a protein coagulum. Coagulation occurs by means of protein denaturation when the blade, vibrating at 55,500 Hz couples with protein, denaturing it to form a coagulum that seals small coapted vessels. When the effect is prolonged, secondary heat is produced, which seals larger vessels. In contrast, electrosurgery and lasers coagulate by burning (obliterative coagulation) at higher temperatures (150 to 400°C). Blood and tissue are desiccated and oxidised (charred), forming eschar that covers and seals the bleeding area. Re-bleeding can occur when blades removed during electrosurgery stick to tissue and disrupt the eschar (Fig. 1).

Ultrasonic energy is an efficient alternative to electrosurgery. Lower temperatures are used with the ultrasonically activated

A



B

Fig. 1 Harmonic Scalpel^{TM} (A) Generator and (B) Scalpel (Ethicon Endosurgery, Cincinnati, OH, USA).

coagulating scalpel, than with electrosurgery. No electricity goes to or through the patient. The surgeon controls the precision of cutting and coagulation by adjusting the power level, blade edge, tissue traction, and blade pressure.

The ultrasonically activated scalpel[25] has led to the development of the ultrasonically activated coagulating shears (CS or LCS). The scissors-like devise has a blunt blade, which oscillates at 55 kHz. This produces heat and vibration and solubilises the collagen in vessels up to 6 mm. CS has simplified operative procedures, reducing operating

time.[34] It is useful in controlling intrahepatic vessels. A disadvantage of the technique is that at a power level of three, it may take 5 to 30 seconds for coagulation to be complete. This may seem tedious compared with simple ligation, in open surgery. CS applied directly to liver parenchyma without the forceps fracture method is also unfeasible as the ultrasonic energy is easily dispersed and not adequately concentrated, resulting in poor coagulation. As long as the blood vessel has enough coagulum material, vessels up to 6 mm may be coagulated.[25] Therefore, it should be able to coagulate most intrahepatic vessels. CS is not good at controlling bleeds from small tributaries or pinholes, however, it is comparable to the forceps fracture method.

WATER JET

The water jet method has been used during hepatic resection. The instrument cuts the hepatic tissue with the high pressure of the fine water flow, while the exposed elastic intrahepatic vessels are spared injury. The jet cutter[26,27,35] produces selective cutting, but the thermal methods cannot discriminate between the vessels and the parenchyma. The loosely connected parenchyma is washed away from the more resilient vessels by shooting a beam of NaCl through a 0.1 to 0.2 nozzle at pressures of 10 to 80 bar. The distance between jet and liver is 1.5 cm and is kept constant by using a suction device. A higher jet pressure is needed to cut the fibrotic hepatic parenchyma. In the case of normal liver, the intrahepatic vessels of more than 0.2 mm are well preserved.

The loss of blood during transaction of the hepatic parenchyma can be easily reduced with a jet pressure of 15 to 16 kg/cm^2. This preserves the fine vessels, more than 0.2 mm in diameter, without injury. When the same pressure is applied in the cutting of a cirrhotic liver, it takes a longer time compared with that of a non-cirrhotic normal liver parenchyma. A disadvantage is the formation of air bubbles, which obscure the operative field. In addition, after the vessels are isolated, conventional ligation or clipping is still required and is time consuming.

CAVITRON ULTRASONIC SURGICAL ASPIRATOR (CUSA)

This is an acoustic vibrator, perfused with saline, which disrupts the liver parenchyma by producing a cavitational force. Diathermy is also in-built into the tip. This has been shown to be very effective for division of parenchyma, with low blood losses.[23,24,36,37] It consists of a hollow titanium tube that vibrates in a longitudinal plane causing selective liver parenchymal destruction. The amplitude of vibration is 100 μm and at a frequency of 23 kHz. Physiological NaCl is used as a coolant. Following division of the parenchyma, any form of vascular occlusion is released. Any residual bleeding vessel on the divided liver surface is controlled. The limitations of CUSA and jet cutting are that after the vessels are isolated, conventional ligation or clipping is still required and is time-consuming (Fig. 2).

Fig. 2 CUSA EXcel^{TM} Ultrasonic Surgical Aspirator (Tyco Healthcare).

RADIO FREQUENCY (RF) ASSISTED LIVER RESECTION (HABIB'S TECHNIQUE)

First described in 2002, this technique uses RF energy to coagulate the liver resection margins.[28] The cool tip probe and a 500 kHz generator produce 100 w of power and enable measurement of generator output, impedance, and tip temperature. The probe contains a 3 cm-exposed electrode, a thermocouple (to measure temperature and impedance), and two co-axial cannulate (through which chilled saline is circulated to prevent tissue boiling and cavitation adjacent to the needle). The generators used in RF thermal ablation are alternating electric current generators that operate in the radio frequency range 200 to 1200 kHz. It is the alternating current that causes thermal injury. The alternating current generator is similar to the electric generator that powers the surgical electric cautery. The primary difference is that, with RF, lower voltage and wattage are used to produce coagulative necrosis. If the tissue is heated too abruptly, as in cauterisation, charring occurs around the electrodes. This markedly limits the size of the thermal injury as a result of the increased resistance. As the ablated tissue dries out, the impedance rises until the electrical circuit is broken (Fig. 3).

In the Habib's technique, initially a line is made on the liver capsule with diathermy to mark the periphery of the tumour, as after RF, the parenchyma is hardened and indistinguishable from tumour. A second line is made 2 cm away from the first line using diathermy,

Fig. 3 RITA Medical Systems — RF Generator.

and RF is applied to the outer line. After the deepest tissue is coagulated, the probe is withdrawn and the cycle repeated. The point of entry of each probe should be 1 cm from the previous. Finally, the liver parenchyma is divided using a scalpel. The division line should be between the two lines so as to leave a 1 cm-resection margin. RF coagulation is applied from within the resection margin, if there is residual bleeding.

FLOATING BALL (TISSUE LINK)

This technology uses a metal probe to deliver RF energy to tissue through an intervening layer of conductive fluid (i.e. saline) infused at the point of tissue contact. The saline solution is infused by means of a ball at the end of the device, coupling RF energy to seal tissue (Fig. 4).

The presence of the fluid dissipates and more evenly distributes the heat during dissection, resulting in tissue temperatures of approximately 100°C. At this temperature the disulphide bonds of collagen molecules break down, causing tissue shrinkage and vessel haemostasis without the smoke production and tissue charring that occur at higher temperatures. Therefore, the side effects of electro surgery that can cause re-bleeding and obscured vision, are prevented. The device gives control to effectively deliver energy into liver parenchyma, enabling pre-coagulation of tissue to be resected. This

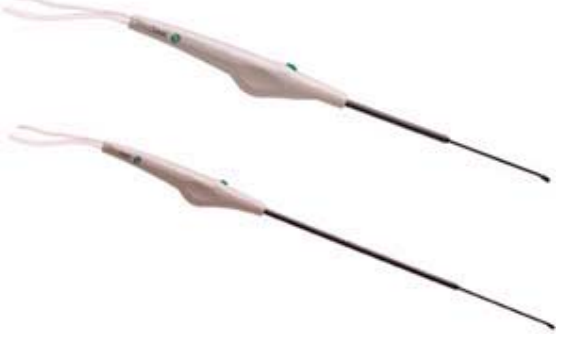


Fig. 4 Tissue Link FB3.0^{TM} floating ball.

creates the possibility of virtually bloodless resections with the potential for less oozing.[38]

TOPICAL SEALANTS

Topical agents have been developed to promote haemostasis such as microfibrillar collagen,[39] bovine collagen-based composite mixed autologous plasma[40] and fibrin sealants.[41,42] Topical sealants are important because they seal vessels and biliary radicles and may reduce common postoperative complications, such as, bleeding and bile leakage. Tisseel (Baxter Healthcare, Deerfield Ill) and Crosseal fibrin sealant have been used in the US and Europe. Crosseal is a new-generation, virally inactivated surgical sealant formulated from a concentrate of human clotting proteins called biological active component (BAC) and a highly purified preparation of human α-thrombin (1000 IU/ml). Fibrinogen is the active component. As Crosseal is human derived, the anaphylactic reactions associated with bovine sealants are avoided. A multicentre, randomised, controlled trial demonstrated that Crosseal was superior to standard treatment haemostatic agents in reducing time to haemostasis following liver resection and reducing complications following surgery.[43]

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Haemostasis in Liver Transplantation Surgery

Raymond M. Planinsic and John J. Fung

INTRODUCTION

Patients with end stage liver disease (ESLD), who are presented for orthotopic liver transplantation (OLT), often have multiple disturbances in haemostasis. These disturbances can result from imbalances in the clotting and the fibrinolytic systems. Excessive bleeding may occur, requiring increased blood product transfusion to replace blood loss due to medical coagulopathy. Occasional thrombotic complications may also occur, leading to potentially catastrophic intravascular or intracardiac thrombosis, cardiac arrest, or death. In addition, use of immunosuppressant drugs at the time of transplantation can have an impact on coagulation.

Intra-operative management of blood loss requires not only exceptional surgical skill, but also an understanding of the derangements in haemostasis. Thrombocytopenia can result from sequestration secondary to portal hypertension and hypersplenism.[1] In

addition, platelet production can be impaired due to chronic disease with diminished thrombopoietin synthesis (natural growth factor for megakaryocytes), and there may be immune-mediated platelet destruction. Malabsorption of vitamin K in patients with cholestatic disease will lead to a decrease in vitamin K dependent clotting factors (Factors II, VII, IX and X). An inability to clear tissue plasminogen activator (tPA) may lead to primary fibrinolysis.[1] This often occurs during the anhepatic phase of the OLT procedure. Primary fibrinolysis, usually manifest by elevated circulating fibrin split products, can be present in critically ill patients when they are first brought to the operating room.

The presence of deficiencies in anti-thrombin III, protein C or S; Factor V Leiden or Factor 11 mutations; anti-phospholipid syndrome; and MTHFR gene mutation must all be considered as risk factors for intravascular thrombosis. This is especially true in patients with known portal vein thrombosis.[2] The imbalance in the haemostatic mechanisms usually leads to excessive bleeding. It is, however, known that patients with primary liver tumours, primary sclerosing cholangitis (PSC), or primary biliary cirrhosis (PBC) tend to be hypercoagulable.[3]

THE NORMAL HAEMOSTATIC MECHANISM

The normal response to vascular injury involves an integrated response among plasma coagulation proteins, platelets, and vascular endothelium. This leads to thrombin generation and formation of a stable haemostatic plug. Exposure of the tissue factor and the extracellular matrix at the site of vascular endothelial injury leads to adherence of platelets to the underlying collagen. This results in activation of platelets, releasing thromboxane and adenosine diphosphate, which attracts and activates additional platelets at the site of vascular injury. In addition, a structural change on the surface of these platelets provides a phospholipid template on which the haemostatic plasma protein cascade may be activated. This ultimately leads to fibrin generation and formation of an integrated platelet-fibrin clot.[4]

Several intrinsic anti-coagulation mechanisms are present both in the plasma and on the vascular endothelial cell surface to prevent clot

propagation beyond the site of vascular injury. Heparan, an endogenous glycosaminoglycan, present on the endothelial surface catalyses the activity of the anti-coagulant anti-thrombin III. A plasma serine protease inhibitor, anti-thrombin III, provides a major mechanism for the elimination of thrombin and other activated coagulation factors from plasma. Tissue plasminogen activator released from the vascular endothelium generates plasmin to degrade fibrin already present. Protein C and Protein S are plasma-derived proteins that modulate coagulation. In addition, thrombomodulin, which is an endothelial cell membrane-bound protein, up regulates the activity of Protein C and alters the pro-coagulant activity of thrombin.[4]

MONITORING OF COAGULATION DURING OLT

Coagulation monitoring is not standardised in centres across the world. The evolution of surgical techniques and coagulation management by anaesthesiologists has significantly decreased the use of blood product transfusions required for OLT. Some centres rely on "traditional clotting studies", such as, prothrombin time (PT), partial thromboplastin time (PTT), international normalised ratio (INR), platelet (PLT) count, and/or fibrinogen levels. Other centres manage coagulation monitoring with thromboelastography (TEG Analyser Hemascope®, Skokie, IL, USA).

When patients with ESLD are first evaluated for OLT, their coagulation status is usually measured by the above listed "traditional clotting studies". Often elevations in PT, PTT, and INR are seen. This is due to decreased synthesis and consumption of coagulation proteins. Platelet counts are usually low due to consumption, hypersplenism, decreased formation, and immune-mediated destruction. Patients with active bleeding can be treated with fresh frozen plasma (FFP) and/or PLT transfusions as indicated.

After patients enter the operating room, rapid diagnosis of clotting abnormalities is essential for quick intervention. Thrombelastography (TEG) is a comprehensive test of whole blood coagulation. It enables measurement of the initial formation of fibrin strands, measured by reaction time (r), within 10 to 14 minutes.[5] Clot formation rate (α) or the speed at which solid clot forms, is normally

53 to 67 degrees and is a function of fibrinogen and platelets. Normal coagulation is represented by a progressive increase in amplitude. It reaches a maximum amplitude (MA) of 59 to 68 mm. MA is a function of the elasticity of the blood clot. The value is increased by improved quality of platelets, fibrinogen, and factor XIII (fibrin stabilising factor). Hartert originally developed the method in 1948, and Kang introduced it to the field of transplantation. Figures 1 and 2 illustrate

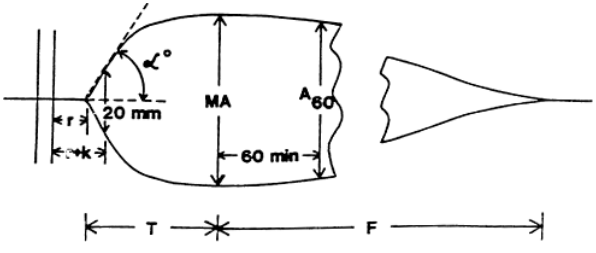

Fig. 1 Thromboelastograph tracing.

R = reaction time 10–14 min
R + k = coagulation time 13–20 min
= clot formation rate 53–67
MA = maximum amplitude 59–66
A_{60} = amplitude 60 min after MA
$A_{60}/MA \times 100$ = whole blood clot lysis index > 85%
F = whole blood clot lysis time > 300 min.

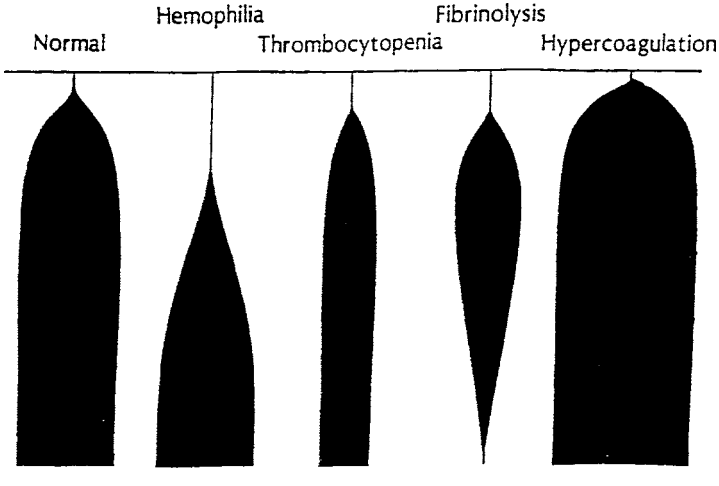

Fig. 2 Various TEG patterns.

the various TEG parameters measurable and the sample tracings of various pathologic conditions.

Thromboelastography provides information on the interaction of PLT, clotting factors, and thrombolytic systems. The patient's whole blood may also be evaluated by the addition of protamine sulfate, epsilon aminocaproic acid, or aprotinin. This will help to detect if there is a significant heparin effect or fibrinolysis contributing to coagulopathy during the procedure. The advantage of TEG is that results are immediately available in the operating room and within 10 to 15 minutes a coagulation defect may be determined and specifically corrected.

INTRA-OPERATIVE MANAGEMENT OF HAEMOSTASIS

Adequate intravenous access is imperative for proper intra-operative management of bleeding during OLT. In addition to large bore intravenous catheters (9 and 8.5 French) for volume and blood product transfusion, an 18-French percutaneous veno-venous bypass (PVVB) cannula is often inserted in the right internal jugular vein.[6] This PVVB cannula can also be used for blood product transfusions. A device that will allow rapid infusion of large volume of warmed fluids and blood products, is indispensable. The FMS 2000® (Belmont Instrument Corporation, Billerica, MA, USA) is such a device that can be used in the transplant procedure. It warms fluid and blood to body temperature, as they are administered to the patient. Rapid infusion (up to 500 ml/minute) of fluids and blood, safely to the patient, is assured with the incorporation of air detectors in the device. It is compact and quiet, and if blood loss is extremely rapid two devices can be utilised simultaneously, in parallel, to enable up to 1000 ml/minute infusion rate. Finally, a blood salvaging system, such as, the Brat 2® (COBE Cardiovascular, Inc., Arvada, CO, USA) cell saver will decrease the requirement for blood bank products.

After an OLT is scheduled, the hospital blood bank must receive a sample of the recipient patient's blood for type and cross matching. A minimal of 10 units of packed red blood cells (RBC), 10 units of fresh frozen plasma (FFP), and a 10-pool unit of PLT should be available before the patient is brought into the operating room.

The transplant procedure itself is divided into three stages. Stage I is the pre-anhepatic or dissection stage; Stage II is the anhepatic stage; and Stage III is the neo-hepatic stage. Stage I extends from the abdominal incision to vascular isolation and removal of the native or diseased liver. Stage II begins when the native liver is effectively removed from the patient's circulation by complete vascular isolation, until perfusion of the donor graft. Stage III begins with reperfusion of the donor graft and ends with closure.

In Stage I, the predominant factors influencing the haemostatic system include pre-existing coagulopathy, clotting factors' dilution, and thrombocytopenia. During Stage II, there is increased fibrinolysis due to absence of the liver. As a result, tPA is not cleared and there are decreased levels of plasminogen activator inhibitor-1 (PAI-1).[1] The onset of Stage III is marked by the development of mild to moderate fibrinolysis. This is noted in approximately 80% of all transplant patients, but severe fibrinolysis with evidence of diffuse bleeding occurs in about 20% of the cases, and this must be treated.[7]

Treatment of coagulopathy requires careful monitoring of the clotting system through TEG or traditional clotting studies, at specific periods during the OLT procedure. The recommended intervals are shown in Table 1. Depending on the duration of the various stages, some of the intervals may overlap (e.g., II + 45 and III − 15) and would require only one study. If TEG is used, additives, such

Table 1. Recommended Clotting Study Intervals During OLT

Interval	Description	TEG Channels
B	Baseline	N
I + 60	Incision + 60 min	N
II − 30	30 min before Stage II	N
II + 10	Stage II + 10 min	N
II + 45	Stage II + 45 min	N + A
III − 15	15 min before Stage III	N
III + 5	Stage III + 5 min	N + A + P
III + 30	Stage III + 30 min	N + P
III + 90	Stage III + 90 min	N
Q 2	Every 2 hrs	N
End	Closure	N

N = Natural, A = epsilon aminocaproic acid, P = protamine.

as, epsilon aminocaproic acid or protamine sulphate to the patient's native or natural blood, may be used to aid in the diagnosis and treatment of coagulopathies.

Use of FFP to replace clotting factor deficiencies is usually indicated and administered when necessary throughout Stages II and I. If significant haemorrhage exists during the procedure, then replacement of blood products with a rapid infusion system will be necessary. Typically, two units of packed RBC, two units of FFP, and 500 ml of normal saline are combined to the transfusion device reservoir to provide the patient with satisfactory levels of clotting factors (> 30%) and haematocrit (26 to 28%).

If fibrinolysis is detected, then small doses of anti-fibrinolytics, such as, tranexamic acid, aminocaproic acid (125 to 250 mg), or aprotinin must be carefully considered.[7–10] If fibrinolysis is significant and fibrinogen levels are depleted, then the use of cryoprecipitate may be indicated. Occasionally, protamine sulfate may be required in Stage III, if the TEG detects a significant heparin effect. This heparin effect is usually self-limiting and resolves by 30 minutes after donor organ reperfusion, in a well-functioning graft.[11]

The optimal regime for aprotinin administration during OLT is still a point of debate. The prophylactic use of aprotinin in a large dose (1,000,000–2,000,000 KIU initial dose followed by 500,000 KIU/h infusion), small dose (500,000 KIU initial dose followed by 150,000 KIU/h infusion), or lower dose (200,000 KIU/h continuous infusion from the beginning of the case without a loading dose) has been recommended by various liver transplant centres in order to control fibrinolysis and reduce blood product transfusions.[12,13] The European Multicentre Study on the use of Aprotinin in Liver Transplantation (EMSALT) showed significant reduction in blood loss and transfusion requirements by 50% and 30%, respectively.[14] These results are a dose-dependent strong anti-fibrinolytic effect and a weaker anti-coagulant effect.[15] Aprotinin is a non-specific serine protease inhibitor with anti-fibrinolytic activity. At low dose it also inhibits plasmin, while at higher doses it inhibits the effects of kallikrein- and leukocyte-derived proteases, such as, elastase.

Other pharmacological agents that have been used in liver transplantation with various levels of success include DDAVP, conjugated

estrogens, recombinant Factor VIIa (Novo Seven®), and Factor VIII/von Willebrand Factor combinations (Humate-P®).[16–18]

PREVENTION AND TREATMENT OF INTRA-OPERATIVE THROMBOSIS DURING OLT

Thrombotic complications, such as, intravascular thrombosis or intracardiac thrombosis occurring during OLT can be catastrophic, causing increased morbidity and mortality. Most of these events occur after reperfusion,[19–22] but have been reported to occur even during the hepatectomy phase of the procedure.[23] Often, these devastating complications may be related to massive blood transfusions, veno-venous bypass use, marginal liver grafts, or hypercoagulability tendencies.

The potential role of anti-fibrinolytics in causing intracardiac thrombus formation during OLT has been described in literature. Use of aminocaproic acid and/or aprotinin, alone or in combination, may have contributed to this problem. Many of these patients had associated pathology, such as, difficult hepatectomy, sepsis (in the weeks prior to transplant), or renal failure (requiring haemodialysis).

Defects in any of the components of the coagulation system may tip the balance between hypo- and hyper-coagulability. Some of the factors associated with an increased risk of thrombosis (thrombophilia) are shown in Table 2.

If intra-operative intravascular or intracardiac thrombosis occurs, treatment options are limited and morbidity and mortality are high. Rapid diagnosis of intracardiac thrombosis is necessary to provide appropriate treatment, and the use of transesophageal echocardiography (TEE) in these situations enables that. Figure 3 shows an intracardiac thrombus that was rapidly detected by routine TEE monitoring of a patient undergoing OLT.[23]

Administration of small doses of heparin to patients with pulmonary embolism has been shown to be beneficial in preventing further clot formation, while enabling endogenous fibrinolysis to proceed.[24] In haemodynamically unstable patients other options include, but are not limited to surgical embolectomy, with or without

Table 2. Factors Associated with Thrombophilia

Platelet	Thrombocytosis
	Platelet concentration of 5-HT
	Platelet glycoprotein IIb-IIIa
Coagulation factors	Fibrinogen
	Von Willebrand factor
	Mutant Factor V (Leiden-G1691A, Cambridge, Hong Kong)
	Mutant prothrombin (G20210A)
	Anti-thrombin III
	Protein C
	Protein S
	Plasmin activator inhibitor
Humoral factors	Lupus anti-coagulant
	Anti-cardiolipin antibodies
	Hyper-homocystinaemia
Clinical factors	Polycythaemia
	Nephrotic syndrome
	Smoking
	Diabetes mellitus
	Obesity
	Oral contraceptives
	Dyslipidaemias

Modified after Fung J., Marcos A. (2003) Rapamycin: friend, foe or misunderstood? *Liver Transpl* 9(5): 469–472.

cardiopulmonary bypass or the use of thrombolytic agents. Both have been described to have a high failure rate.[19]

Prevention of intravascular or intracardiac thrombosis during OLT should be the goal. Patients undergoing OLT have been shown to elevate levels of endogenous heparinoids.[25] Patients at an increased risk of thrombophilia or demonstrating a hypercoagulable TEG (see Fig. 2) should be given low dose heparin (2000–5000 UI). This is especially necessary if veno-venous bypass is used during the OLT procedure.[23] Low dose prophylactic use of heparin in OLT has been shown to prevent pulmonary thromboembolism and is not associated with excess bleeding.[26] The risk and the benefit of anti-thrombin III and activated Protein C administration is not yet proven in clinical trials, but the decision to use these agents empirically can be based on clinical judgment.[27,28]

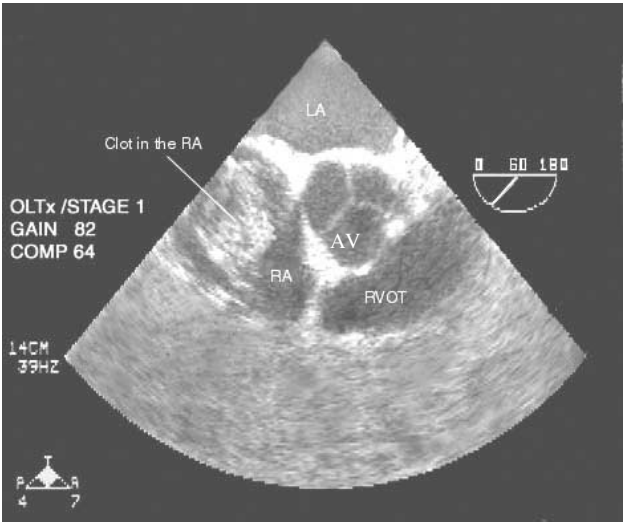

Fig. 3 TEE mid-esophageal right ventricular inflow-outflow view (RA, right atrium; LA, left atrium; AV, aortic valve; RVOT, right ventricular outflow tract). After Planinsic R. *et al.* Diagnosis and treatment of intracardiac thrombosis during orthotopic liver transplantation.[23]

EFFECTS OF IMMUNOSUPPRESSANTS ON COAGULATION DURING OLT

An increased risk of thrombosis is associated with some of the immunosuppressant agents. Cyclosporine, for example, has been associated with elevated fibrinogen level, increased platelet aggregation, and von Willebrand factor changes.[29] In addition, corticosteroids have been associated with increased plasminogen activator inhibitor activity.[30] Some studies have debated if the use of sirolimus, in combination with cyclosporine or tacrolimus, is associated with an increased risk of hepatic artery thrombosis.[4,31–33]

Induction therapy with polyclonal anti-thymocyte-globulin (ATG) is widely used in the prophylaxis and treatment of acute allograft rejection. Thrombocytopenia, however, is a major side effect of ATG therapy, and its mechanisms are poorly understood. In Ankersmit's study, the influence of ATG on platelet aggregation was examined aggregometrically.[34] Expression of platelet surface activation antigens, CD62P and CD63, was determined by flow cytometry analysis.

Electron microscopy was utilised to determine thrombocyte morphology. Treatment of platelets with ATG markedly induced aggregation, effect that was completely blocked by antibodies against the low-affinity Fc IgG receptor (CD32). Blocking of CD32 abrogates platelet aggregation, therefore, the authors suggest that CD32 plays a crucial role in ATG-induced thrombocytopenia.[34]

Campath 1H (C1H) is a humanised monoclonal antibody directed against the CD52 antigen that is present on the surface of T cells, B cells, NK cells, and monocytes. It depletes the peripheral blood lymphocytes, preventing an aggressive lymphocytic immune response after transplantation. Adverse events include acute first-dose administration-related reactions (attributed to antibody-induced cytokine release), infectious complications (due to immunosuppression), and haematological toxicities. Rigor, fever, nausea, vomiting, skin rash, dyspnea, and hypotension are among the most commonly reported infusion-related reactions with alemtuzumab. thrombocytopenia, anaemia, and neutropenia are the most common haematological alterations.[35]

CONCLUSION

Patients presented for OLT have multiple medical problems in addition to ESLD. Underlying disturbances in the normal haemostatic mechanism result from imbalances in the clotting and the fibrinolytic systems. Understanding the impact of co-existing disease and the physiological and the metabolic changes that occur throughout the various stages of the OLT procedure, is essential. In addition, precise monitoring of the haemostatic mechanism is required for optimal outcome. Improvements in surgical technique and management of the coagulation system by anaesthesiologists have decreased surgical time, blood loss, transfusion requirements, and adverse outcomes.

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Haemostasis in Kidney and Pancreas Transplantations

Muhammad Tariq Dosani and Nadey S. Hakim

INTRODUCTION

The surgical technique of kidney transplantation has not changed significantly since the first transplants were performed. The improvements in dialysis, antibiotics, immunosuppressive medications, and postoperative complications management have, however, markedly improved patient and graft survival. As the success rate improved, the indications for renal transplantation continued to expand, so that it is now the preferred treatment for most patients with end-stage renal disease. Transplant recipients present new technical challenges because the population is ageing and the number of patients with prior surgical procedures is increasing.

The demand for renal transplantation has also resulted in an expansion of the criteria for acceptable donor organs. The anatomical variability of donor organs and recipients requires meticulous surgical technique at the time of organ recovery and transplantation,

to minimise technical failure. Haemostasis is vital in these patients, especially when they are uraemic and already on dialysis. It is a known fact that kidney failure patients are more prone to bleeding and are frequently started on anti-coagulants in the perioperative period.

LIVE DONOR NEPHRECTOMY

Most of the kidneys for transplantation, across the world, come from living donors. A potential kidney donor must volunteer to donate and be in excellent health without risk factors for end-stage renal disease.[1] If the donor is immunologically suitable, studies like magnetic resonance angiography (MRA) are done to evaluate the vascular anatomy. Selection of the side of the donated organ depends on the imaging findings. The left kidney is selected when the donor has a bilateral single vessel or bilateral multiple vessels. The operation is performed under general anaesthesia. A Foley catheter is inserted and prophylactic antibiotics are given. The patient is placed in the right/left lateral position on the operating table. The kidney rest is elevated, and the table is flexed to maximise exposure to flank. The kidney is approached through a mini anteriolateral flank incision (7 ± 2 cm in length) located at the last intercostals space, without resection of the rib. Using the Omni-tract retractor, an adequate operative field is created within the retroperitoneal space. This enables sufficient handling of the kidney. For the stapling and the division of the vessels and the ureter, the ETS-FLEX endoscopic linear vascular cutter or ELVC (ETHICON ENDO-SURGERY, INC, USA) is used.[2] When positioned on a vessel the ELVC applies three staple lines proximally and three distally, and the vessel between them is divided. The distal end of the ELVC, which has the staples, can be rotated to fit perfectly on a vessel regardless of the angle. Before or after dissecting the vessels, the ureter is stapled and divided. The ELVC is applied initially to the main renal artery and, subsequently, to smaller arteries, if present. It is then applied to the main renal vein followed by smaller renal veins, if present. In our experience, this is the most efficient way of haemostasis. The previous method, involving hand sewn closure of the vascular stumps, was risky and time consuming. With the use of the stapler, perfect haemostasis is achieved. There is no bleeding

whatsoever. Prior to clamping the vessels, 5000 IU Heparine is given bolus IV followed by a reversal with 50 mg of protamine following the removal of the kidney. The kidney is flushed after the removal of staple lines. At our centre, senior author has been using the vascular cutter for the past five years, and it has given excellent results with no postoperative haemorrhagic complications.

LAPAROSCOPIC DONOR NEPHRECTOMY

Laparoscopic techniques minimise the morbidity and reduce the disincentives to living donor nephrectomy.[3] Laparoscopic procedures significantly reduce postoperative pain and hospitalisation period. They also reduce the loss of time until able to work. Operative time and cost are, however, increased. Of greater concern is a slightly higher rate of kidney loss, dysfunction, and ureteric stenosis. Renal vessels can be quite short, which may make the renal transplant procedure technically more difficult. The effects of pneumoperitoneum, which may decrease the renal blood flow, and a brief period of warm ischemia on the long-term allograft function are not yet known. Haemostasis is similar to the open surgery using the same staplers. The operative risk of bleeding is similar however it can be a challenging to deal with severe bleeding at time of dissection.

CADAVERIC DONOR NEPHRECTOMY

The majority of organs obtained for cadaveric transplantation are from patients who are brain dead. Most cadaveric donors are suitable for multiple organ retrieval. The organs are removed in the order of their susceptibility to ischemic injury. Therefore, the heart and the lungs are removed first, followed by the liver and the pancreas and, finally, the kidneys. A midline incision is used to expose the medisatinum and the peritoneum. The organs are carefully examined for signs of disease and vascular anomalies. Canulas are placed in the ascending aorta for the cardioplegia solution and the abdominal aorta for the organ preservation solution. The organs are, then, rapidly cooled and flushed. In the obese donors, it is important to ensure that iced saline is in contact with the kidney surface to prevent

warm ischemic injury while the other organs are removed. The vena cava is carefully divided above the renal vein orifices, and the aorta is divided between the superior mesenteric artery and the renal artery orifices. After the liver has been removed, the ureters are divided in the pelvis and gently mobilised with a generous amount of peri-ureteral tissue to prevent injury to the delicate ureteral blood supply. The kidneys are mobilised from the retroperitoneum and removed en bloc with both adrenal glands. They are placed in basin with iced saline solution, and the left renal vein is separated with a cuff of vena cava. The aorta is divided in the midline, and the renal arteries are identified. Next, the anterior aorta is divided to separate the kidneys. The retroperitoneal adipose tissue is excised from the convex surface to exclude disease and assess the adequacy of perfusion. The kidneys are sterile. They are placed in preservative solutions and, then, packed in ice.

TRANSPLANT PROCEDURE

After a suitable donor kidney has been obtained and the histocompatibility has confirmed the absence of a serologic crossmatch reaction, the transplant recipient is notified. Blood samples are sent for routine investigations. If the International Normalised Ratio (INR) is greater than two, anti-coagulation is reversed with fresh frozen plasma. At least two units of crossmatch negative packed red blood cells are ordered. This also applies to the donor procedure. Blood transfusion in the donor is very unusual and more likely in the recipient in view of the uraemic status.

BENCHWORK PREPARATION

Preparation of cadaveric kidney is essential to minimise haemostatic and other complications. The kidney is removed from its sterile container, placed in ice-cold sterile saline, and thoroughly inspected. The perinephric fat, muscle, lymphatics, and the adrenal gland are removed without injuring the renal vessels or the ureter. It is best not to dissect too close to hilum. Vessel branches that do not lead to or from the kidney are ligated. Arterial branches are completely

dissected away from the kidney prior to ligation, to ensure that the branches do not supply the kidney or the ureter. Small venous branches may be ligated as there are multiple intracollaterals. In living donation, these steps are a part of the dissection prior to ligation of the vessels. In cadaveric donors, the vena cava and the aorta are trimmed to create a cuff around the orifice to facilitate the vascular anastomosis. When the right kidney is used, there tends to be a significant difference between the length of the short renal vein and the long renal artery. Many surgeons use the vena cava to extend the right renal vein, to make up for this discrepancy and prevent kinking of the artery.[4] Others cut the renal artery short and perform an end to side anastomosis without a Carrel patch.[5] Multiple renal arteries occur in approximately 25% of the kidneys. It is usually best to fashion a large patch of the aorta known as carrel patch, which includes of all them. If the patch is too long, it may be possible to cut an intervening segment of the aorta or reimplant a polar vessel into a larger renal artery.[6] The kidney is stored in the iced saline until revascularisation.

TRANSPLANT PROCEDURE

Following the induction of general anaesthesia, catheter is inserted. It is connected to an antibiotic containing saline solution. A hockey stick incision is made in the lower quadrant of the abdomen. The right side is usually used for a first transplant as the iliac vein is more superficial. To expose the iliac vessels the inferior epigastric vessels are divided, the peritoneum is swept medially, and the spermatic cord is mobilised (in females, the round ligament is divided). An Omnitract is positioned to maintain exposure. The renal vein or the caval extension is anastomosed to external iliac vein, in an end to side fashion. All the lymphatics are ligated with suitable suture material to prevent lymphocele. The donor renal artery or, in the case of cadaveric kidney, the Carrel patch is anastomosed to the external iliac artery in an end to side fashion, using an aortic punch to create an arteriotomy.[7] After the vascular connection is complete, the vascular clamps are released. If necessary, additional sutures are placed to obtain haemostasis. This is not likely to be required, however, if

meticulous suturing is done using optical loops. Next, the kidney is positioned in the retroperitoneum to avoid kinking of the vessels, and the ureter is anastomosed to bladder in a meticulous way so that haematuria does not occur. Haematuria can be a major problem and require blood transfusion.

HAEMOSTATIC TOOLS

Vascular Closure Staples

Use of the vascular closure staples (VCS) in kidney and as well as in liver and pancreas transplantation is well documented.[5,8] Use of the VCS contributes in creating an excellent anastomosis and minimising operative time. The excellent results from our experience with the use of VCS for vascular access encouraged us to use them in kidney and pancreas transplantations. The vascular closure staples create an excellent anastomosis and minimise warm ischaemia time. Therefore, they contribute to haemostasis.

Chemical Haemostatic Agents (Surgicel)

Chemical haemostatic agents like surgicel are often using in transplant surgery, because these products control bleeding without occluding the vessel lumen and cause no thermal injuries to adjacent structures. A topical haemostat is often the technique of choice to control bleeding in the case of diffuse capillary and venous oozing. These haemostats have been used in surgical procedures for more than 30 years, however, new application forms like Surgicel fibrillar and Surgifoam powder entail different handling options.

Use of Protamine

The use of heparin is a more important consideration, especially in the case of longer warm ischemic time. Protamine sulfate to reverse heparin anti-coagulation during donor nephrectomy is a useful technique to reduce both intra-operative and postoperative bleeding complications.

VASCULAR COMPLICATIONS

Vascular complications are seen in less than 10% of renal transplant recipients, but they are an important cause of graft dysfunction. In contrast to other causes of transplant dysfunction, vascular complications have a high associated morbidity and mortality. After vascular lesions are identified, it is usually easy to the repair them.

Traditional angiography used to be the standard for the diagnosis of vascular complications, however, ultrasound performed with duplex and colour Doppler modes is an excellent non-invasive modality for evaluating the affected vessels. This followed by the MRA (Magnetic Resonance Angiography), which is also non-invasive.

Renal Artery Thrombosis

Renal artery thrombosis is a rare complication in transplantation that is more common in kidneys with donor vascular disease or with multiple vessels requiring bench surgery before transplantation. It is also common in kidneys from paediatric en bloc donors. Other possible causes include persistent hypotension, dehydration, and procoagulant conditions (e.g., lupus anti-coagulant and diabetes). It can be an acute event postoperatively or up to a few months postoperatively. Reasons for early arterial thrombosis are usually technical. Fine vascular suture materials should be used for the anastomosis. We usually use 5/0 Prolene for the vein and 6/0 Prolene for the artery. If the allograft does not perfuse properly the vascular clamps are re-applied, the kidney flushed with cold perfusion solution, and the anastomosis redone. In delayed arterial thrombosis salvage is rarely possible. The patient may experience severe pain, swelling, or severe haematuria. There may be cessation of urine output or an episode of severe rejection. Thrombosis can be identified with Doppler and allograft nephrectomy is usually required.

Renal Vein Thrombosis

Renal vein thrombosis usually occurs in the early postoperative period. It can be due to kinking of vessels or due to stenosis at the anastomotic site. Hypotension, acute rejection, and hypercoagulable state

are other causes. If renal vein thrombosis occurs intra-operatively, allograft will appear swollen and cyanotic. Thrombectomy and revision of anstomosis can salvage the kidney. In the case of delayed thrombosis, thrombolytic therapy with intravenous anti-coagulation may be of help.[9] The usual outcome of renal vein thrombosis is infarction, and a transplant nephrectomy is usually performed to prevent infection.

Lymphocele

Lymphoceles usually occur four to eight weeks after surgery and affect up to 15% of patients. The cause of these collections is possibly the disruption of the normal lymphatic channels during perivascular dissection or the disruption of hilar lymphatics. Most lymphoceles are discovered incidentally and are asymptomatic. Most of them also do not require therapy. Lymphoceles, however, have the potential to exert mass effect and, therefore, can impair renal function by producing hydronephrosis or cause conditions, such as, oedema of the leg, abdominal wall, scrotum, or labia. Lymphoceles can be treated with either percutaneous or surgical techniques. In our series, lymphoceles are almost inexistent as we take the time to ligate all the lymphatics during the dissection of the recipient vessels. This is a type of "lymphostasis" as it is of utmost importance to complete to prevent any side effects of the lymphoceles.

Renal Artery Stenosis

Renal artery stenosis is the most common vascular complication in transplantation, reported in up to 10% of patients. Potential causes include recipient artery arteriosclerosis, donor artery atherosclerosis, renal artery kinking, surgical arterial injury, faulty surgical technique, rejection, and clamp injury. Percutaneous transluminal angioplasty and stenting is the treatment of choice.[10] Surgical intervention is required in difficult cases. Intra-operative haemostasis is vital during the initial surgery. If bleeding is encountered while fashioning the anastomoses and extra suturing is required, stenosis can be iatrogenically induced and cause future chronic problems.

Intrarenal Arteriovenous Fistulas and Pseudoaneurysms

Intrarenal arteriovenous fistulas and pseudoaneurysms are the result of vascular trauma during percutaneous biopsy. Arteriovenous fistulas may form when an artery and vein are lacerated; pseudoaneurysms result when only the artery is lacerated. These can occur after renal biopsies that could be traumatic. The majority of these lesions are small and clinically insignificant. They usually resolve spontaneously, therefore, the frequency of this complication is unknown. When lesions are sizable, marked arteriovenous shunting may result in renal ischaemia. Haematuria or perigraft haemorrhage may result when large arteriovenous fistulas or pseudoaneurysms rupture. When symptomatic or large, intrarenal arteriovenous fistulas and pseudoaneurysms may be effectively treated with embolisation.

HAEMOSTASIS IN PANCREAS TRANSPLANTATION

The principles discussed above, also apply to pancreas transplantation. The most important step in pancreas transplantation is the benchwork preparation of the organ. We have been regularly using the vascular stapler ETS-FLEX endoscopic linear vascular cutter (ETHICON ENDO-SURGERY, INC, USA)[2] for pancreas benchwork. This has not only improved haemostasis, but has significantly shortened our procedure time. This, in turn, is translated into better graft function. The pancreas is very vascular. It also contains numerous microvessels that can bleed in the postoperative period and lead to large haematomas. These can compress the vasculature of the organ and cause graft thrombosis. This remains a significant postoperative complication in pancreas transplantation, especially in the solitary pancreas transplants.

To conclude, haemostasis in kidney and pancreas transplantations is of utmost importance as it translates into immediate graft function and uneventful postoperative recovery.

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Haemostasis in Endocrine Surgery

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INTRODUCTION

Endocrine surgery, like all areas of surgery, relies on adequate haemostasis, which is a vital part of any surgical operation. Serious morbidity and even mortality can occur due to inadequate control of bleeding. The most well-documented complication of haemorrhage in endocrine surgery occurs with bleeding following thyroidectomy. This results in a rapid rise in pressure within a closed space, which can threaten the airway and even the life of the patient.

In a hospital setting postoperative monitoring and emergency treatment for haemorrhage is possible, but with the expansion of day surgical services, where bleeding may occur at home, adequate haemostasis becomes even more critical.[1] Postoperative bleeds requiring a return to theatre occur in 0.5 to 1% of patients, with 75%

occurring within the first 4 to 6 hours and 25% within 7 to 24 hours. Haemorrhage can also occur later.[2]

Meticulous haemostasis is vital in minimally invasive surgical procedures, where access and surgical view is limited. Blood will obscure the operative field, and in the case of endoscopic operations will also absorb the light, making surgery more hazardous.

OPTIONS FOR HAEMOSTASIS IN ENDOCRINE SURGERY

Physiologically, haemostasis at its simplest involves vascular spasm, platelet plug formation, and clotting, with subsequent limitation of acute haemorrhage. Vascular spasm, triggered by damage to a vessel, is insufficient by itself to arrest blood loss. Platelets, which circulate freely in the blood, are exposed to the tissue collagen of the damaged vessel wall and not only stick to the breach, but also to each other.

Simultaneously platelets release a number of chemical mediators, such as, adenine diphosphate (ADP) and products of arachidonic acid metabolism, such as thromboxane A2. This further contributes to platelet stickiness, resulting in the formation of a platelet plug, occluding the opening in the vessel wall. Platelet plugs are inherently insecure structures that are subsequently anchored in place by the formation of a fibrin clot. Clotting is dependant on a group of plasma proteins called clotting factors, most of which are synthesised in the liver by Vitamin K-dependant reactions. They are normally present as inactive pro-enzymes, which when activated, proceed down a proteolytic cleavage pathway (intrinsic or extrinsic clotting pathways) resulting in the conversion of prothrombin to thrombin.

Thrombin catalyses the conversion of fibrinogen to fibrin monomers and their subsequent polymerisation into cross-linked fibrin strands. The resulting clot traps erythrocytes and bridges the opening in the vessel, securing the platelets in position. In time, clot retraction pulls the damaged edges of the blood vessel together.[3]

Any technique that augments a part of this pathway, whether it takes a mechanical, electrical, or chemical form will assist in the control of haemostasis. In the authors' experience however, there is no substitute for meticulous surgical technique. In this chapter we aim

to cover both novel and well-established techniques of haemostasis used in endocrine surgery.

Mechanical Methods

Sutures and ties

The simplest and longest established method of haemostatic control in the field of endocrine surgery is the use of absorbable sutures and ties. Some surgeons advocate their use in the neck to the exclusion of all other haemostatic methods, although this view has become outmoded by newer technologies now available to the surgeon.

Suturing can be a valuable adjunct for haemostasis of the thyroid remnant after subtotal resection of the thyroid, for fixing the capsule of the gland to the pretracheal fascia. Similarly, absorbable sutures can be used for controlling troublesome bleeding from damaged anterior jugular veins. Absorbable sutures are recommended rather than silk, as adverse reactions have been reported with the latter.[4]

Titanium clips

Another method of securing small vessels is with the Ligaclip (Ethicon Endo-surgery, Cincinatti, Ohio, USA), a titanium metal clip that is inexpensive, inert, and compatible with magnetic resonance imaging. These clips should be used in the correct size for the vessel being ligated, but in experimental studies can secure vessels to well above physiological levels of blood pressure.[5–7] The potential for dislodgement has led the authors to use double rather than single clip applications.

Oxidised cellulose

Surgicel (Johnson & Johnson, Somerville, New Jersey, USA) is a resorbable oxidised cellulose material that can be placed into the thyroid wound before closure. It comes prepared as a sterile fabric meshwork that becomes fully absorbed with blood, swelling to a brown gelatinous mass that aids in clotting. Its mechanism of action

is, however, unclear and may be physical rather than altering the clotting pathway.[8]

Surgicel has been found to be bactericidal *in vitro* because of its acidic pH and is also effective against antibiotic-resistant microorganisms.[9] It has been suggested to cause adhesions under experimental conditions, which may make its use in the neck problematic, especially when second operations are possible.[10,11] Its use does not, however, lead to increased risk of infection.[12,13]

ActCel (Coreva Health Sciences, California, USA) is a relatively new haemostatic agent made from a similar meshwork cellulose fabric as Surgicel. It is also indicated for haemostasis from open wounds and body cavities. In contact with blood, it expands to four times its original size, converting to a gel. It is completely dissoluted in 1 to 2 weeks and because its end products are water and glucose, wound healing is not affected.

Electrical/Heat Methods

Electrocautery

Surgical diathermy is the mainstay of haemostatic control of small vessels and is convenient, quick, and relatively safe to use. The authors favour the use of monopolar diathermy forceps, where current passes through the active electrode, causing a localised heating effect before passing through the patient to the dispersive electrode (patient plate). It is of paramount importance that there is a large surface area contact of the plate electrode to prevent damage to tissues other than where the active electrode is applied. The coagulation setting is preferred, which produces less heat and coagulates proteins and desiccates cells, rather than cell explosion and destruction that occur with the cutting setting. The authors will generally perform a thyroidectomy using diathermy alone as the haemostatic method, and rarely need to use ties or other aids to haemostasis.

Diathermy is not without potential hazards, however, as high energy electrical currents are passed through the body. The possibilities include interference with pacemaker function, heating effects with metal implants, and superficial burns as a result of spirit-based

skin preparation or patient earthing through contact with metal or inappropriately applied patient electrodes.

Bipolar diathermy is inherently safer as current is passed between the tips of a pair of insulated forceps and less energy is required. It has limited efficacy, however, other than in the control of bleeding from very small blood vessels, and cutting is not possible.

Ultrasonic shears

The Harmonic Scalpel (Ethicon Endo-surgery, Cincinatti, Ohio, USA) uses ultrasonic technology that enables both cutting and coagulation at the precise point of impact. This instrument controls bleeding by tamponading the vessel and sealing it with a protein coagulum at temperatures ranging from 50 to 100°C. Coagulation occurs by means of protein denaturation, when the blade, vibrating at 55,000 Hz denatures the protein to form the coagulum seal. In contrast, electrocautery coagulates by burning at much higher temperatures, forming an eschar seal.

The advantage of the harmonic scalpel is that it offers greater precision in tight spaces near important structures, although the authors feel that the currently available hand piece is too large and cumbersome for use in the neck. The Harmonic Scalpel is also currently a relatively expensive piece of disposable equipment. Ultrasonic dissection, however, has a vital place in the abdomen in the laparoscopic approach to adrenal and pancreatic endocrine surgery. It is the authors' favoured method for dissection and excision of insulinomas and other pancreatic endocrine tumours, and it has made laparoscopic adrenalectomy safe and feasible.

Potential benefits of ultrasonic haemostasis compared with electrosurgery include less lateral thermal damage,[14] minimal smoke, and no risk of electric shock. The blade of the ultrasonic shears can, however, heat up quickly to high temperatures and damage the recurrent laryngeal nerve during surgery. Therefore, the blade should not be used closer than 3 mm from the nerve.[15] The shears should always be used on a lower power setting and with short activation times to prevent collateral damage.[16]

Ligasure

Ligasure (Valleylab, Boulder, Colorado, USA) is a vessel sealing system that fuses vessels up to 7 mm in diameter without dissection or isolation and with minimal lateral thermal damage. It is a bipolar, computer controlled diathermy system that uses pressure and energy to create a seal by melting the collagen and the elastin in the vessel wall and reforming it into a permanent, plastic-like seal that does not rely on a proximal thrombus. Thermal spread is less than 1 mm with the Ligasure Precise instrument that is used in the neck, but thermal spread increases with vessel size.[17] This is important in determining the device's safety around the recurrent laryngeal nerve and external branch of the superior laryngeal nerve. There was no difference in thermal spread between the Ligasure and the Harmonic Scalpel, and both systems have equal efficacy in securing vessels up to 7 mm in size to well above physiological levels of blood pressure.[5,18]

Studies of its results in thyroid surgery suggest that the Ligasure device is an effective and safe alternative, with faster operating times and possibly a lower risk of hypoparathyroidism when compared with conventional clamp-and-tie thyroidectomy.[19–23]

Haemostatic Agents

Fibrin sealant

Fibrin sealants, such as, Quixil (Johnson & Johnson Wound Management, UK) are biological haemostatic agents derived from human plasma. Two components are mixed together on application; the first component contains fibrinogen and the second component is a solution of thrombin, and calcium required to activate coagulation. Their action imitates the final stages of the clotting pathway, which converts fibrinogen to fibrin. The resulting clot aids haemostasis and tissue sealing and is subsequently absorbed during wound healing. Therefore, any foreign body reaction or extensive fibrosis is avoided.

Fibrin sealants have not been studied well in thyroid surgery,[24–26] but have been widely used in many areas of surgery to obtain haemostasis. They are easy to handle, rapidly absorbed, and have a haemostatic action independent of the general clotting mechanism.

They appear to have similar complication rates compared to conventional techniques and lead to lower drainage output after thyroidectomy.[26]

ENDOCRINE SURGICAL PROCEDURES

Thyroid and Parathyroid Surgery

Thyroid and parathyroid procedures can be considered together as they involve surgery in the same area of the neck, and the haemostatic techniques are generally the same. For convenience, they may be divided into preoperative, intra-operative, and postoperative measures.

Preoperative

All patients should stop aspirin, low molecular weight heparin, and similar medication likely to interfere with platelet function, at least one week beforehand. These simple measures will reduce the risk of postoperative ooze into the thyroid bed and prevent haematoma formation within the wound, which may take several weeks to resolve. After resolution of a haematoma, the scar may be tethered and unsightly and may need re-excision to improve the cosmetic appearance.

The patient should be positioned comfortably on the operating table with the neck extended, to enable good access to the anterior compartment of the neck. This is normally achieved by placing a pillow or bag of fluid under the shoulder blades and stabilising the head on a rubber ring or horseshoe. Care must be taken in patients with cervical bone disease. In patients with short stocky necks or large goitres, the chin can be elevated by tape strapping to the table and the shoulders can be depressed by gentle traction of the arms. Tape can also be used to strap down the breasts if this is contributing to a confined operating space. Good theatre lighting and the use of a bright white xenon operating headlamp is essential for adequate illumination and visualisation of important structures, particularly in the case of minimal access techniques. Prior to skin incision the table

should be tilted to 15° head up, to reduce engorgement of the neck veins.

Endocrine anaesthesia plays a crucial role, particularly in the use of hypotensive techniques, to maintain the blood pressure at 20% below normal levels. This reduces intra-operative bleeding. Careful preoperative assessment is undertaken to ensure that there are no pre-existing cardiovascular problems that may preclude such a technique.

Prior to incision of the skin, some surgeons infiltrate the area with local anaesthetic or adrenaline solution in an attempt to reduce bleeding. This is not favoured by the authors, however, as much of the bleeding at the skin edges will stop with direct pressure and more persistent bleeding points are best recognised and dealt with at the time with diathermy. It can also contribute to a false sense of security as it may take some time for the vasoconstrictive effects to wear off, risking subsequent bruising and formation of a wound haematoma.

Intra-operative

Most procedures are carried out through a traditional, Kocher collar incision placed a finger's breadth above the supraclavicular joint. Minimal access techniques tend to use a portion of this same incision.

After the skin incision has been made with the scalpel, the authors use a monopolar diathermy forceps with foot pedal operation to dissect carefully through subcutaneous fat and platysma, although this dissection can be carried out with scissors (Fig. 1). Care must be taken to avoid the anterior jugular veins that course beneath the fascial layer. If they are damaged or are in the way of surgical access, they are best divided by clamping with artery forceps and tying with 2/0 absorbable ties. The key is to locate the bloodless plane between platysma and the fascial layer in front of the strap muscles to keep blood loss to a minimum.

A diamond shaped surgical field is created by mobilising the skin flaps superiorly as far as the thyroid cartilage and inferiorly to the suprasternal notch. It is maintained by a self-retaining Joll's retractor. The approach least likely to cause bleeding is between the strap muscles in the midline, which is achieved by incising the midline raphe with monopolar diathermy or scissors. The strap muscles,

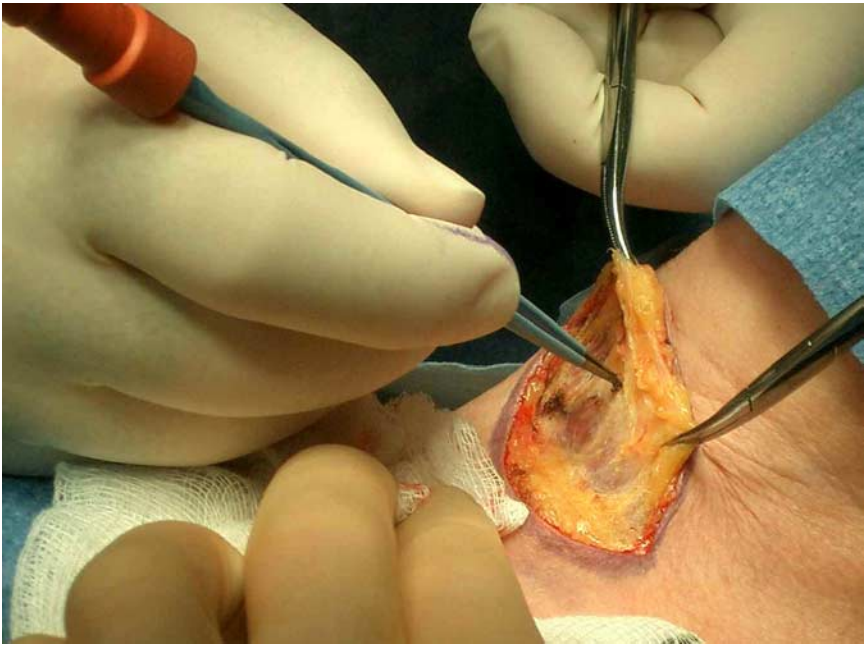

Fig. 1 Raising of superior skin flap with monopolar diathermy forceps.

which may have become very atrophic as a result of a large goitre, may either be retracted or in the case of a very large gland, divided with diathermy. Care should be taken to avoid damaging a fairly constant vessel between the two strap muscle layers at the upper end of the field. The sternothyroid muscle is, then, dissected from the thyroid gland, ligating the middle thyroid vein with diathermy, ligaclips, or ties.

It is important to identify the recurrent laryngeal nerve before removing the thyroid or the parathyroid, finding it low in the neck and following its course upwards to the larynx. All the authors' patients undergo preoperative vocal cord checks and intra-operative recurrent laryngeal nerve monitoring. The authors use a Neurosign 100 nerve stimulator (The Magstim Company, Wales, UK) in conjunction with a laryngeal electrode attached to the endotracheal tube (Fig. 2). The electrode is not surgically invasive and is manufactured using a flexible polyester substrate with conductive ink tracks to measure the EMG activity. The laryngeal electrode is connected

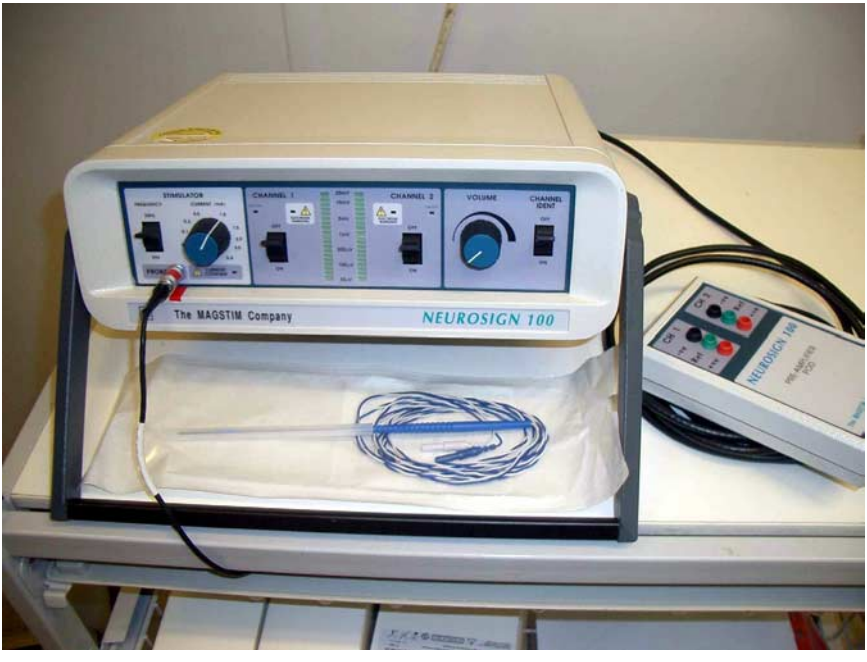

Fig. 2 Neurosign 100 nerve stimulator and probe.

to the pre-amplifier pod and a bipolar stimulating probe used to deliver a high stimulation current (0.5 mA to 1 mA) to the recurrent laryngeal nerve. The authors feel that intra-operative nerve monitoring is a vital adjunct to safe neck surgery, and before any use of the diathermy or other haemostatic measure, the nerve should be located.

If both lobes of the thyroid are to be removed, then the larger lobe is generally removed first, making mobilisation of the other lobe easier. The superior pole of the thyroid, with superior thyroid artery and veins are dealt with first. Care is taken to avoid damage to the external branch of the superior laryngeal nerve. By staying on the thyroid and carefully ligating the terminal branches of the artery, haemostasis is easily achieved and safer than mass ligation.

Similarly, when mobilising the lower pole of the thyroid, the main trunk of the inferior thyroid artery is not ligated as this vessel supplies the parathyroids, but the terminal branches are found on the thyroid

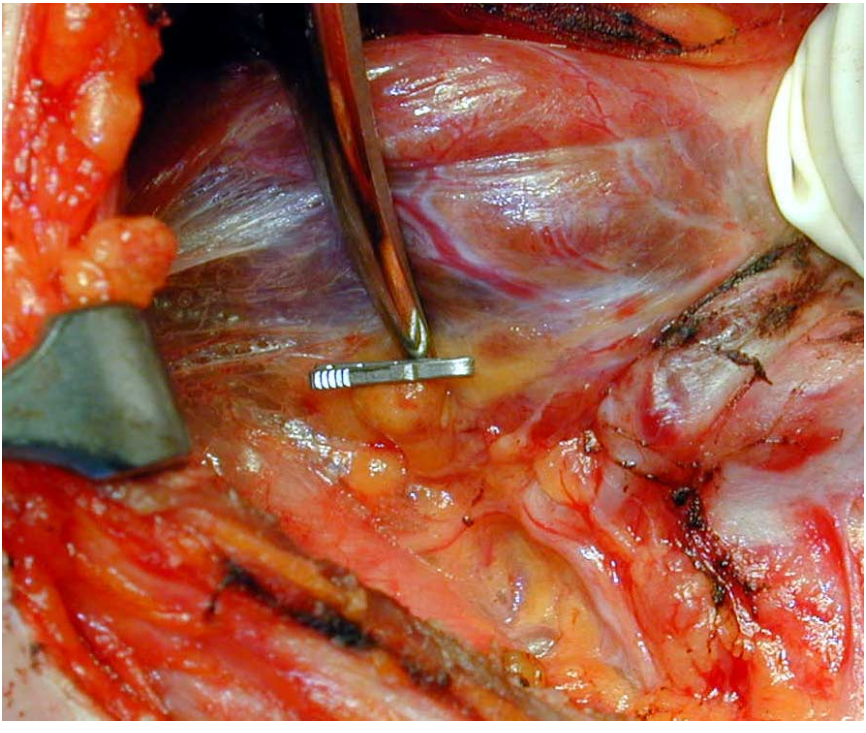

Fig. 3 Ligaclip marking right upper parathyroid gland at tip of forceps (recurrent laryngeal nerve is also visible).

and ligated. This has the bonus of being much safer for the recurrent nerve as well. At this stage the parathyroids are sought and preserved, their position marked with a small ligaclip (Fig. 3). If enlarged, as in the case of a patient with hyperparathyroidism, they are removed for frozen section confirmation.

After the lobe has been fully mobilised, the vessels ligated and divided, and the recurrent laryngeal nerve and parathyroids identified, the thyroid is removed. The authors favour using monopolar diathermy alone to divide these small terminal branches of the main vessels and to dissect the lobe free from the pretracheal fascia. The key to this technique is to stay very close to the thyroid, with judicious use of a combination of diathermy and gentle traction, sometimes aided by the use of a stay suture.

If there is difficulty with bleeding, pressure with a pledget or dry swab for five minutes will normally control most small vessels. Diathermy in the thyroid bed can have grave consequences for the nerve, particularly if the view is somewhat obscured by haemorrhage, so ligaclipping or underrunning of bleeding points with an absorbable suture is better. Washout of the cavity created by lobectomy and, then, a dry swab left in place will control most oozing while the other side is removed.

In the case of parathyroid disease or thyroid cancer it may be necessary to perform a cervical thymectomy. This should be relatively simple to perform with few complications and virtually no bleeding, provided the appropriate technique is used. The thymus has a distinct structure to it compared with the surrounding fat and has a small vessel on its posterior surface, which must be cauterised or ligated. The thymus is separated from the thyroid by dividing the thyro-thymic ligament that is used to pull the thymus up from the mediastinum with sustained and steady traction (Fig. 4). Thymectomy should be virtually bloodless, but if there is any bleeding from the thymus bed, a dry swab left for five minutes will almost always control it.

It is essential that haemostasis is secured prior to closure of the wound. This is best achieved by identifying bleeding from vessels only when the venous pressure has been raised. The authors have the patient placed in a 15° head-down tilt position with the anaesthetist performing a Valsalva manoeuvre (expiration against a closed glottis) to 30 cm of water. This will often identify small vessel bleeding that would otherwise be missed and become the cause of a haematoma in the postoperative period when anaesthetic hypotensive effects have worn off or if the patient coughs after extubation.

If the patient has undergone subtotal resection, there may be troublesome bleeding from the thyroid remnant, which can be controlled by suturing to the pretracheal fascia with an absorbable suture. If the dissection has been extensive or a large vascular goitre has been removed, a suction drain may be used, but routine use is unnecessary. Drainage offers little relief from poor haemostasis, and it will not prevent a patient with significant bleeding in the neck from having to return to theatre.

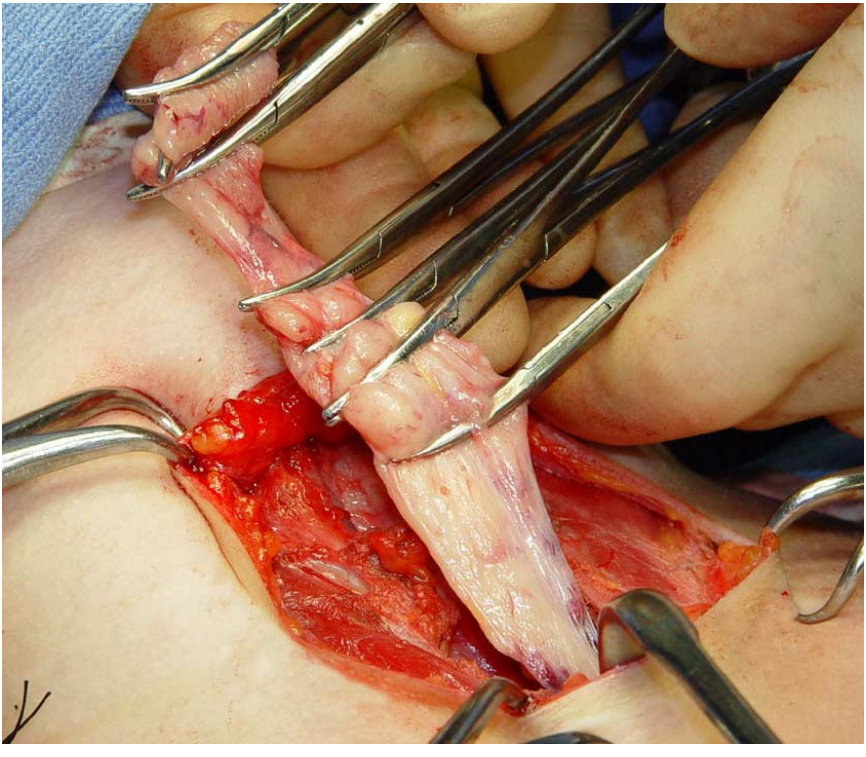

Fig. 4 Excision of the thymus from the anterior mediastinum by gentle traction.

Closure of the wound comprises approximating the strap muscles with an absorbable suture, taking care not to inadvertently pierce one of the anterior jugular veins. In the authors' practice, the platysma is then closed, the wound infiltrated with bupivicaine with 1 in 200,000 adrenaline, and the skin closed with interrupted 4/0 nylon.

Postoperative

The wound is dressed with steristrips and a low allergenic, non-adherent dressing. The authors favour the application of a mild pressure dressing around the neck for 24 hours, to diminish oozing. All patients are encouraged to sit up to reduce venous engorgement, and drains, if present, are usually removable within 48 hours of surgery.

Sternal split and mediastinal exploration

Sternotomy may be indicated for the removal of a large retrosternal goitre or mediastinal parathyroid or the excision of a thymoma in a patient with myasthenia gravis. Meticulous planning is undertaken preoperatively to localise tumours so that the minimum amount of time is spent exploring the chest. This also reduces trauma and potential blood loss. It is usually not necessary to split the whole sternum, but only the manubrium (Fig. 5), which gives adequate access for exploring the aorto-pulmonary window in the case of ectopic parathyroid excision.

During the procedure diathermy is usually adequate for haemostasis, but the cut edges of the sternum can produce troublesome bleeding. The authors' practice is to use bone wax for control. It is a sterile mixture containing beeswax and paraffin and achieves local haemostasis by acting as a mechanical barrier, tamponading small vascular channels in the bone.

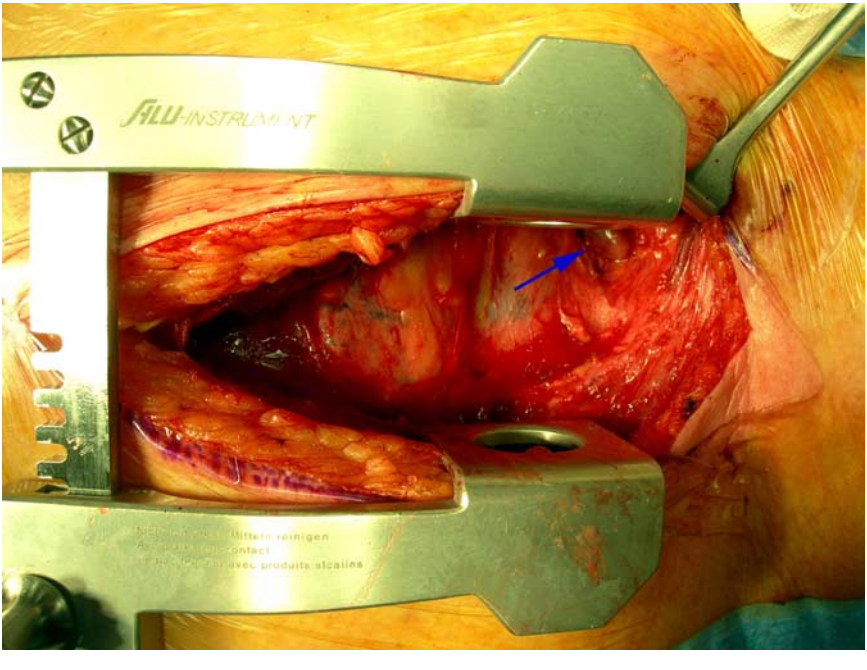

Fig. 5 Manubrial sternal split revealing an ectopic parathyroid gland (at tip of arrow).

Bone wax has no biochemical action and is minimally resorbable. This means it may have possible adverse effects on osteogenesis and can produce mild inflammatory reactions. It acts as a mechanical barrier, therefore, it may prevent clearing of bacteria from infected sites. This is, however, rarely a problem in elective endocrine surgery.[27] A review by Milano *et al.*[28] found no evidence of bone wax causing mediastinitis and noted that poor haemostasis was, in fact, the major contributor to a higher risk of infection.

Adrenal Surgery

Functional and non-functional adrenal disease forms a relatively small part of any endocrine surgery practice, with adrenalectomy accounting for less than 10% of the operative workload. Resection of the adrenal gland is ideally suited for a laparoscopic approach because open removal requires a relatively large incision for retrieval of a small gland, with greater morbidity and mortality as a result. Improvements in endoscopic instrumentation and technique has meant that most adrenal surgery can now be performed laparoscopically, the main criteria for an open approach being a tumour greater than 6 cm in diameter and the presence of malignant disease. The unit policy in fit patients is to remove any functioning adrenal tumour and any incidentaloma greater than 4 cm in diameter.

Adrenalectomy preparation

Laparoscopic adrenalectomy is safe and effective if the surgeon has a thorough knowledge of the anatomy, and the patient is rendered endocrinologically safe prior to any surgical procedure. This is particularly important in the case of phaeochromocytoma and in Conn's syndrome, where the patient must be pre-treated with appropriate drugs to block the excess hormone effects. Anaesthesia for these patients is highly specialised and should only be undertaken by those with appropriate training and experience.

Conn's syndrome patients require electrolyte abnormalities and hypertension to be corrected by administration of spironolactone prior to surgery. Patients with phaeochromocytoma must have

alpha-adrenergic blockade, with or without beta blockade, to prevent dangerous episodes of hypertension during adrenalectomy. Both require some weeks of stabilisation on medications, which will make hypertension less likely and diminish the risk of excessive blood loss during surgery.

There are a variety of approaches to the adrenal gland, either open or laparoscopic and via transperitoneal or retroperitoneal routes. The most common laparoscopic approach and the favoured route of the authors, is transperitoneal, with the patient in the lateral decubitus position. The retroperitoneal approach has the advantage of a more direct route to the adrenal vein, but is a technically demanding operation for a surgeon more familiar with intraperitoneal anatomy. The open approach tends to be via the transperitoneal route, rather than the retroperitoneal route through the bed of the 12th rib. For very large tumours access can be improved by extending the incision into a thoracoabdominal approach, but this is rarely required.

Laparoscopic adrenalectomy

Like laparoscopic cholecystectomy, the approach to the adrenal gland via the laparoscopic route has clear advantages over open operation. The absence of an upper abdominal incision results in less postoperative pain, lower blood loss, and faster recovery.[29] Approximately 60% of adrenal operations can be undertaken with the laparoscope, the main exclusions being large tumours and those suspected or proven malignant.[30] Three or four ports are required, depending on the side of the operation, plus a liver retractor, a multi-fire ligaclip applicator, and a suction irrigator apparatus. Care must be taken, as in any laparoscopic operation, to avoid abdominal wall vessels when placing the access ports. Bilateral laparoscopic adrenalectomy can be undertaken by turning the patient and redraping between sides.

The anatomy of the adrenal gland would suggest that it is a very vascular organ, with three separate arteries and, often, two veins. In practice, however, the arteries are small and not easily identified. They rarely require formal ligation, with only the inferior adrenal artery likely to need ligaclipping.[31] The dissection is performed using

the ultrasonic shears or a laparoscopic diathermy hook, which give excellent haemostasis. The main adrenal vein tends to be singular, and control is normally achieved through multiple ligaclip ligation. There have been some reports of clip dislodgement with associated bleeding, particularly if the adrenal vein is short.[32] This danger can be overcome using extracorporeal ligation of the vein or by the application of an Endoloop (Ethicon Endo-surgery, Cincinatti, Ohio, USA) suture. An accessory adrenal vein may be emptying into the hepatic veins from the superior aspect of the adrenal, therefore, care must be taken during this aspect of the mobilisation to ensure haemostasis.

Partial adrenalectomy is possible for patients with small, potentially benign tumours, such as, aldosterone-producing adenomas. This means that the patient has a lower risk of functional deficit after adrenalectomy. Additional care must be taken, however, to secure haemostasis of the cut edge of the gland. Generally, the use of the ultrasonic shears is sufficient or, alternatively, a vascular stapler can be used.[33] If there is an oozing raw surface, the application of fibrin glue may help to prevent haematoma formation.[34]

The operation is completed by removal of the specimen in a bag, which should be extracted by enlarging one of the port sites to prevent rupture of the bag and spillage of the contents. The placement of a surgical drain is rarely required, and it can usually be removed after 24 hours. Port removal should be performed under direct vision to check for bleeding from an abdominal wall vessel that may have been tamponaded during the procedure.

Open adrenalectomy

The indications for open adrenalectomy have been narrowing rapidly as experience with the laparoscopic technique has evolved. The open approach is now confined to patients with larger tumours and suspected or known malignancy. In the authors' unit, none of the past 85 laparoscopic adrenalectomies required conversion to open operation because of the careful case selection of appropriate patients preoperatively.

Open adrenalectomy can be performed via a posterior, loin, or anterior transperitoneal approach. The authors favour an extraperitoneal posterior approach through the bed of the 12th rib, providing the most direct route to the adrenals. It is also a useful approach in patients who have had previous abdominal surgery and are likely to have complex and difficult adhesions. If the tumour is very large a thoracoabdominal incision can be used, but is very rarely needed. The open transperitoneal anterior approach can be necessary for bilateral adrenalectomy in Cushing's syndrome, but laparoscopic approaches are now favoured if possible.

Pancreatic Endocrine Surgery

The majority of endocrine tumours of the pancreas are insulinomas and gastrinomas, but a variety of other tumours are also seen, with differing clinical syndromes related to their hormone secretion. These syndromes can result in life-threatening illnesses, such as, the profound hypoglycaemia of insulinoma and the debilitating ulcer disease of gastrinoma, due to over production of hormone.

After the clinical syndrome of the excess hormone production has been recognised, a process which can take years, appropriate investigations can be undertaken to confirm the diagnosis and localise the tumour. Besides the non-invasive imaging modalities, the authors favour all patients undergoing angiography and calcium-stimulated venous sampling for accurate localisation and subsequent safe and successful surgery.

The only curative treatment for patients with insulinoma and gastrinoma is surgical resection. In the authors' unit the preferred approach to resection of an insulinoma is either laparoscopic enucleation or laparoscopic distal pancreatectomy, while gastrinomas, which are often located in the duodenal wall, are generally removed by open surgery. Intra-operative ultrasound (IOUS) is a vital adjunct, particularly in laparoscopic resection, to check on the position of small tumours not readily visible to the surgeon. It will locate 90 to 95% of insulinomas, and when combined with preoperative localisation with calcium-stimulated angiography and venous sampling, result in a cure in nearly all patients.[35,36] IOUS enables visualisation

of the tumour's relationship to the main pancreatic duct (MPD) and vessels, as there is a higher risk of pancreatic fistula if enucleation is undertaken of a tumour abutting the MPD.[36]

Laparoscopic resection of insulinoma

The laparoscopic approach to the pancreas is with the patient lying supine and with four or five ports placed to enable full mobilisation of the pancreas, if necessary. Haemostasis can be achieved with either hook diathermy or with ultrasonic shears, but the latter is preferred. After a window is opened in the gastrocolic ligament, laparoscopic ultrasound can be performed to localise the tumour and determine the relative safety of enucleation versus distal pancreatectomy.[37,38]

Enucleation of an insulinoma is reserved for benign, solitary tumours, less than 2 cm in diameter, located on the surface of the pancreas and not in contact with the MPD, main splenic vessels, or portal vein. Enucleation can be performed with ultrasonic dissection that will control small pancreatic vessels, supplemented by the application of ligaclips, if necessary. After the tumour has been removed and placed in a bag for extraction, the bed is closely inspected for haemorrhage and pancreatic leak, the latter occurring in approximately 18% of patients.[37] Additional suturing and application of fibrin glue may diminish the risk of haemorrhage and fistula formation, but there is little evidence to support this as yet[39] and is not the practice of the authors.

If the tumour is close to the MPD and there is no margin of normal pancreatic tissue, then distal pancreatectomy should be undertaken, preferably laparoscopically and with preservation of the spleen. The transaction of the pancreas is performed with a laparoscopic linear stapler (EndoGIA, US Surgical, Norwalk, CT, USA) that will control vessels within the parenchyma and the MPD, but additional intracorporeal suturing or use of ligaclips may be required. Fibrin glue can be applied at the discretion of the surgeon, but there is no evidence that this reduces the rate of fistula formation. Splenic vessels can be readily controlled with ligaclips or the harmonic scalpel.

Open resection of endocrine tumours

Both enucleation and distal pancreatectomy for insulinoma can be undertaken as open procedures, utilising the same surgical principles and techniques for haemostasis, as in laparoscopic resection. Gastrinomas are usually approached at open surgery, however, because of the likely location of the primary tumours in the duodenum and the possibility of metastatic spread to local lymph nodes. Routine duodenotomy and palpation of the duodenal wall increases the detection rate of gastrinomas, which may be multiple, and it makes cure more likely.[40]

Gastrinomas may be found anywhere in the gastrinoma triangle (Fig. 6), therefore, good access is required to the whole of the upper abdomen, including the whole of the pancreas, regional lymph nodes, and liver. Primary tumours are frequently small, most commonly in the proximal duodenum, and associated with regional lymph node metastases in 60% of patients.[41] Approximately 10% of cases have primary gastrinomas within lymph nodes, without any identifiable primary tumour.[42] An extensive exploration is required, including duodenotomy and palpation, plus routine removal of local

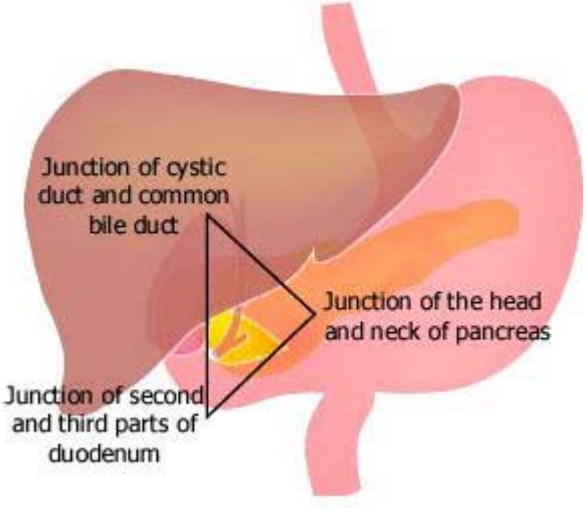

Fig. 6 Diagram of the gastrinoma triangle.

nodes. This can be safely achieved with conventional techniques of haemostasis, with sutures, ligaclips, and diathermy.

Pancreatic and duodenal operations, either laparoscopic or open, require drainage to deal with any potential pancreatic leakage that might become secondarily infected and have the potential for secondary haemorrhage.

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Haemostasis in Urology

Shabnam Undre and Anup Patel

INTRODUCTION

Inadequate haemostasis is one of the most important causes of morbidity and mortality following urological surgery. The increase in the number of day-case procedures performed and the rapid expansion of minimal access surgery have highlighted the importance of ensuring both meticulous surgical technique and haemostasis. The possibility of contaminated blood products and the hazards of blood transfusion are further stimuli for the avoidance of unnecessary blood transfusion. In this chapter, we have covered some conventional and some new techniques to achieve haemostasis in urological procedures.

HAEMOSTASIS IN UROLOGY

Renal Surgery

Percutaneous renal surgery

Percutaneous renal access for bulky stone disease involves a controlled trans-parenchymal stab into the collecting system. Haemorrhage is one of the most significant potential complications of percutaneous nephrostolithotomy (PCNL).[1] This complication may be reduced by accurate pre-planning of the tract location either by ultrasonography, 2-D fluoroscopy, mixed ultrasonographic and fluoroscopic guidance, CT, or spiral CT (3-D).[2] Bleeding can occur from the renal parenchyma when rigid dilators are serially passed or after dilatation of the access tract causes splitting of a narrow calyceal neck. Use of a balloon dilator as opposed to rigid dilators may reduce the incidence of bleeding during track dilation. The use of periodic screening during tract dilatation to check the position of the dilator tip is recommended to help prevent complications during this stage of the procedure. For the most part, access tract parenchymal bleeding can be controlled sufficiently to permit safe working conditions, by using the next size up of dilator fitted with a co-axial sheath. This serves to tamponade small and medium sized vessels, but such a manoeuvre may worsen venous bleeding from a split calyceal neck. It is rarely necessary to control bleeding from the track by using a double lumen nephrostomy tamponade catheter, where the first balloon retains the catheter within the collecting system while a longer balloon inflated at pressure provides tamponade.[3] If significant bleeding is encountered during stone manipulation (often in obstructed, infected systems), the procedure may have to be abandoned due to poor visualisation and to prevent fluid absorption through open vessels. In this situation, it is important to recognise this fact early on without compounding the problem of complicated access and leave a nephrostomy tube of sufficient size *in situ* for at least a week (our preference is to leave a 3-way 24 Fr. Foley co-axially over a 6 Fr single J stent placed down the ureter over the safety guide wire). After the bleeding has stopped and a mature track has formed, a second look usually ensures a successful outcome. Postoperative

bleeding through the nephrostomy tube may be halted by temporarily clamping the tube. This acts as a tamponade, and unclamping is done several hours later by which time the bleeding should have stopped by normal clotting mechanisms.[1] Bleeding that does not respond to this conservative treatment may require renal angiography and selective or sub-selective arterial embolisation.[1] Open exploration is generally undertaken only in the case of failure of all other modalities, as it often leads to partial or total nephrectomy.[1,4] If open surgery is required, provided no further potentially infected stone material remains, betadine soaked Dacron patches can be used as bolsters to anchor the sutures into the potentially friable parenchyma, using deep vertical mattress sutures.

Renal trauma

In case of renal trauma, the majority of penetrating injuries and a small percentage of blunt injuries (Grade II to V), resulting in laceration or vascular injury with a haemodynamically unstable patient, will require surgical intervention. Peterson suggests that surgical intervention should be avoided unless bleeding is life threatening, as in most cases this results in a nephrectomy,[5] except in centres of excellence where considerable experience has been gained by sub-specialist urologists. Cass holds the opposite view and recommends early surgical management of major lacerations with or without extravasation.[6] It is difficult to assess the correct management as no group has compared operative and non-operative management in a controlled, randomised fashion at a single institution. If an operative route is preferred, the key step is to obtain vascular control by identifying the pedicle early on. If necessary, vascular clamps may be applied after adequate hydration and intravenous administration of a diuretic, such as, mannitol, before the haematoma is cleared away to give adequate exposure.[7] Haemostasis is then achieved on the lacerated margins by using a monofilament absorbable suture on a fine tapered needle. This needle is placed in a figure of eight over the bleeding points, if the capsule is intact. It is then sutured over a gelatin foam sponge. If the capsule has been destroyed an omental pedicle flap or Dacron mesh may be used to close the defect. Fibrin sealant is

also an effective and a safe topical agent for control of surface bleeding during elective and trauma related urological procedures. It has been used successfully for haemostasis during renal reconstruction.[8] Fibrin glue is made by combining a solution of fibrinogen concentrate and factor XIII with a solution of thrombin and calcium.[9,10] It is very useful in securing haemostasis, controlling haemorrhage, and sealing anastomoses.[11] A disadvantage of this agent is that it requires an almost dry surface before application and, therefore, deep injuries may pose a problem. In contrast an agent, such as, FloSeal® may provide immediate and durable haemostasis and does not require a dry parenchymal surface.[12]

Nephrectomy

The key to safe working around major vascular structures in the renal hilum is to ensure that all the relevant anatomy is visible and has been clearly identified. It is also essential to ensure adequate visualisation of the inferior vena cava above and below the entry site of the right renal vein, before it is secured. Be wary and look out for abnormal anatomy. Azygous or hemi-Azygous veins may drain directly into the renal vein. Therefore, one must check carefully with adequate retraction, for these anomalies before applying slings or ties. Furthermore, there should be no tension on the vessel when tying sutures. This is necessary to avoid the uncomfortable experience of avulsing the vessel inadvertently and causing torrential bleeding (particularly when tying veins connecting to major structures, such as, the inferior vena cava) and to ensure that one is right on the adventitial layer of the vessel if it is to be clipped. Being on the adventitial layer is important because the surrounding fat may interfere with secure clip application, leaving the lumen partially open. If a vessel, particularly a large vein, is avulsed vascular clamps and sutures may be necessary. Often, however, if the vessel is not large it can be temporarily controlled by the application of an atraumatic Babcock clamp. An open tipped suction device together with the assistance of an experienced anaesthetist is useful at this time. On the left side, it is important to protect the spleen from injury during any retraction of the upper part of the wound. During open nephrectomy, bleeding from the renal bed may be difficult to control due to the nature of the bleeding, which is often

multi-focal capillary or venous ooze. In these circumstances, local haemostatic agents can be a useful alternative to packing the wound. Materials that have been used for this purpose include absorbable haemostatic gelatin sponge, cellulose, collagen, FloSeal,® and fibrin glue. These agents act primarily by causing platelet aggregation on contact or by stimulating blood coagulation.[9]

Major renal vessels may be secured during laparoscopic or open nephrectomy by applying a series of clips on the "stay side". This is to ensure that the vessel will remain secure even if one of the clips were to be dislodged. In other words, a haemostasis "wall of steel" would be in place (Fig. 1). In modern practice, regular metal clips that are easily dislodged have been replaced by locking plastic clips (e.g., Weck clips). In open surgery, a Vicryl ligature may also be applied proximal to the clips before the vessel is divided. Other electrosurgical devices have also been developed for sealing vessels up to 5 mm in size. There is a haemostatic system (LigaSure®, Valleylab, Boulder, CO, USA) that works by tissue coagulation and enables fast, effective, and

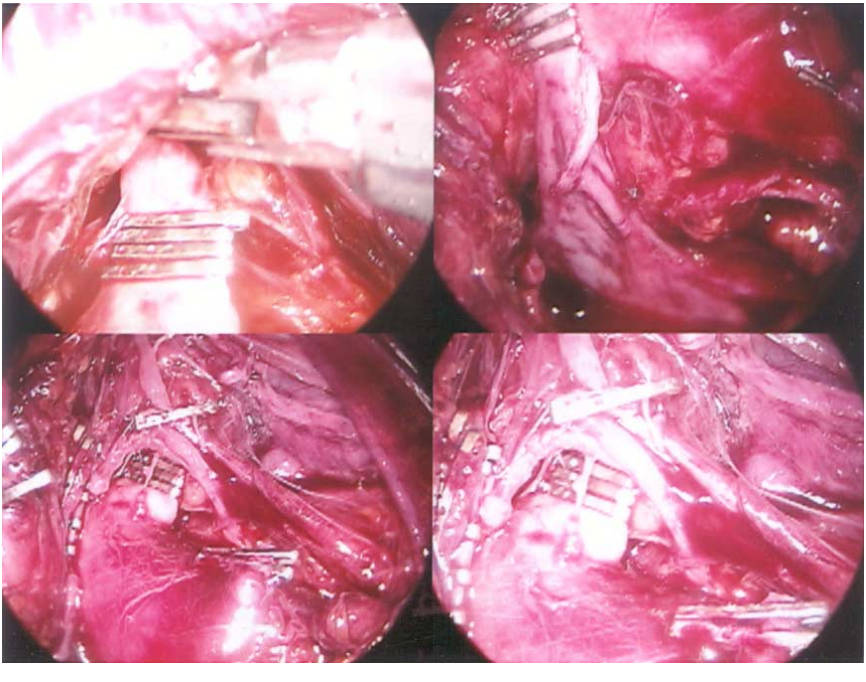

Fig. 1 "Wall of steel".

safe haemostasis in complex urological surgery.[13] It may be used for haemostasis during nephrectomy. It is a computer-controlled bipolar diathermy system, which uses radio frequency current applied under pressure. It is designed to optimally seal vessels that are less than or equal to 7 mm in diameter, with minimal lateral thermal damage. It is reported to minimise blood loss and save time[14] and is available in the form of different instruments for different applications (Fig. 2).

During laparoscopic nephrectomy, the renal artery is controlled with metal clips, locking plastic clips, or devices, such as, the LigaSure.

Fig. 2 Liga-Sure and application of Liga-Sure.

Fig. 3 Roticulating and straight Endo-GIA.

The renal vein may be secured by any of these or with the Endo-GIA vascular stapler (Fig. 3).

For nephrectomies, where there is extension of the tumour into the IVC (inferior vena cava), proximal and distal vascular control should be gained. Then, cavotomy with extraction of the tumour thrombus is performed. Ligature, patch closure, or vena cava segmental replacement (where tumour invades the wall of the vessel, thankfully, a rare event) may be required in some cases. If the

thrombus extends into the intrahepatic portion of the vena cava or above, extensive exposure and isolation of the cava are required and, possibly, mobilisation of the liver, cardio-pulmonary bypass (CPB), or deep hypothermic circulatory arrest (DHCA).[15] Bleeding during vena caval surgery is usually encountered from the lumbar veins draining directly into the back of the vessel, leading to steady ooze even when the lumen has been secured between proximal and distal clamps. The key to safe progress under these circumstances is good preparation of sutures and equipment and adequate suction. Sufficient experience to carry out the required manoeuvres in an expeditious manner after the vessel has been opened, is also vital. This is not an operation for the occasional practitioner and should be carried out in a centre of expertise.

Partial nephrectomy

Partial nephrectomy or nephron sparing surgery has been associated with bleeding due to the highly vascular nature of the renal parenchyma. Several suggestions and devices have been used to try and minimise this bleeding.

For partial nephrectomy, the use of biological glue that consists of gelatin, resorcinol, and formaldehyde,[16] has been suggested as a successful haemostatic agent. Shekarriz and Stoller described the use of fibrin sealant for controlling surface bleeding during partial nephrectomy.[8] Studies on animals have concluded that the use of an absorbable fibrin adhesive bandage facilitates partial nephrectomy by reducing blood loss and ischaemic and total operative times.[17] In addition, haemostasis has been successfully achieved by the use of biodegradable hydrogels in porcine models.[18]

Laparoscopic and open partial nephrectomies have been performed using FloSeal®, a two-component tissue sealant consisting of a gelatin matrix granular component and a thrombin component. This was applied after resection of the tumour, before perfusion of the kidney, and it provided immediate and durable haemostasis.[12] It acts by activating the coagulation cascade, while maintaining a haemostatic plug that is not easily displaced. During blood contact, the gelatin particles swell and produce an effective tamponade.

A new ready-to-use haemostatic agent, TachoComb® (Nycomed Austria GmBH, Linz, Austria), consisting of a collagen sheet coated on one side with human fibrinogen, bovine thrombin, and bovine aprotinin has also been successfully used in surgical operations, including urological surgery.[19]

The application of argon beam coagulation is an alternative to conventional methods of haemostasis whenever there is a diffusely bleeding operative site, such as, in partial nephrectomy for penetrating trauma.[20] The argon beam coagulator acts by producing thermal injury to large surface areas where current constantly arcs to sites of low impedance, leading to eschar formation and delayed tissue necrosis. The argon beam coagulator can also be used to perform the capsulotomy and to weld gelfoam onto the cut surface of the kidney in nephron sparing surgery, as described in an animal model.[21] The argon beam coagulator has also been used with oxidised regenerated cellulose gauze for haemostasis following laparoscopic nephron-sparing surgery using ultrasonic shears. It has shown good results for small, solid renal masses.[22]

Microwave tissue coagulation through the use of percutaneously inserted antenna probes has been used during partial nephrectomy in experimental models. It has been shown to reduce blood loss and operative time, and it also poses minimal risk of vascular injury.[23]

A novel technique has been described for watertight closure and minimal parenchymal bleeding following partial nephrectomy. This involves the use of porcine small intestine mucosa (SIS).[24]

Laparoscopic partial nephrectomy has been performed in animal models using an arcing-gap electrosurgical snare. Excellent haemostasis was achieved, and there was no need to control the renal vasculature. In most cases, the haemostasis was adequate with the snare alone. In one case, additional haemostasis was required using the argon beam coagulator.[25]

Retroperitoneoscopic nephron-sparing surgery using a microwave tissue coagulator has also been performed, for small renal tumours. Minimal blood loss occurred.[26] This surgical tool is based on the principle that by radiating a 2450 MHz (12 cm wavelength) microwave from a monopolar antenna within tissue, the heat generated will be limited to within the electromagnetic field

generated around the antenna. This will lead to coagulation of protein in that field.[27]

Hydro-jet cutting is an advanced technology that has been used to create an ultra-coherent water force, which functions like a sharp knife. This technique enables selective parenchymal cutting with preservation of vessels. Coagulation can be applied, as required, via a bipolar thermo-applicator. This technique, when used for partial nephrectomy, improves haemostasis and offers a bloodless operating field with a clear view. It has been described in experimental models and in humans for laparoscopic nephrectomy.[28,29]

ESWL

Bleeding can be an uncommon complication of ESWL. It is more likely in a patient with uncontrolled hypertension or those with established coagulopathy. Recombinant activated factor VII (Novo Seven®) was used successfully in a case where the patient suffered a large subcapsular and peri-renal haematoma following ESWL. The bleeding was stopped, and there was no obvious accompanying coagulation disorder.[30]

Renal transplant

Acute postoperative haemorrhage may occur due to disruption of a vascular suture line. It may also occur due to inadequate preparation of the graft bed, undetected or poorly ligated branch of the hypogastric artery, inappropriately ligated epigastric vessels, unrecognised vessel in the renal pelvis, abnormal coagulation mechanisms of the recipients, and spontaneous graft rupture.[31] The incidence is increased when dialysis is required in the immediate postoperative period. After diagnosis, urgent emergency re-exploration is usually necessary. If vascular repair or reconstruction cannot be accomplished within a reasonable time, then allograft nephrectomy is indicated. Evacuation of the haematoma is important to prevent bacterial infection.[31]

Adrenal Surgery

Adrenal surgery, for the majority of benign disease indications, is performed laparoscopically. Haemostasis is primarily achieved through clip application for the adrenal veins and clips or cauterisation for the adrenal arteries. For partial adrenalectomy, haemostasis can be achieved by bipolar coagulation and, finally, sealing with fibrin glue.[32] Laparoscopic partial adrenalectomy, involving the use of a vascular stapler has been described. It also achieved perfect haemostasis.[33] In cases where significant intraperitoneal scarring is anticipated from prior abdominal surgeries, adrenalectomy may be performed by a trans-thoracic trans-diaphragmatic approach. This avoids both bleeding complication and bowel injury from the division of multiple adhesions.

The safety of endoscopic adrenalectomy depends on careful dissection and appropriate haemostasis. There have been several reports of haemorrhage due to dislodgment of clips, following adrenalectomy. When only short length of vessel is a limitation on the number of clips that can be applied safely, one way to overcome this problem is by using a technique which involves open looping of the vessel with a 2-0 dacron suture preloaded on a plastic push-rod (Surgiwhip®, U.S. Surgical Corporation, Norwalk, CT), exteriorisation of the loop, and tying of a Tayside knot. This knot is then slipped, locked, and tightened in place. A square knot is then fashioned with the two tails of the Tayside knot, using an intracorporeal technique, to add holding strength (Fig. 4).[34]

Ureters

Fibrin sealant has been successfully used for haemostasis, in addition to anastomosis or reconstruction of the ureters.[8] Iatrogenic perioperative injury of a ureteric artery (which is a very rare condition) can be successfully managed by percutaneous interventional techniques, with trans-catheter embolisation. This embolisation may be performed using micro particles, coils, glue, or gelfoam depending on the anatomical configuration of the injured vessel. In one reported case, 350 to 500 μm polyvinyl alcohol particles were used to control

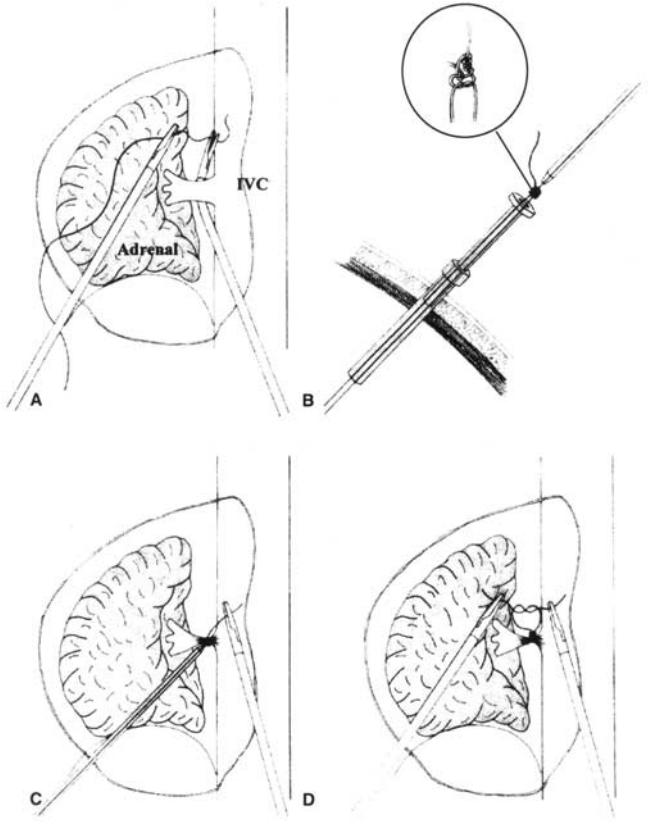

Fig. 1. Operative steps involved in the ligation of the main right adrenal vein. **A** The coaxially curved grasper is passed behind the vein. **B** The Tayside knot is tied with the exteriorized limbs of the loop. **C** The rod is pushed with simultaneous traction on the tail. **D** A square knot is added.

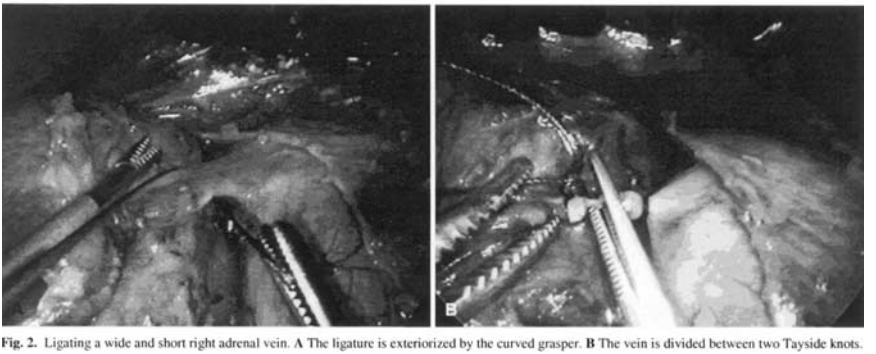

Fig. 2. Ligating a wide and short right adrenal vein. **A** The ligature is exteriorized by the curved grasper. **B** The vein is divided between two Tayside knots.

Fig. 4 Reproduced with permission from Sir A. Cuschieri and Springer *Surg Endosc* (1999) 13: 298–302, Safety of adrenal vein ligation during endoscopic adrenalectomy, A. Pietrabissa, A. Cuschieri, A. Carobbi, U. Boggi, F. Vistoli and F. Mosca.

retroperitoneal haemorrhage caused by injury to a lower ureteric artery.[35]

Bladder

Open surgery

Radical cystectomies have been associated with significant blood loss, due to the many vascular pedicles that have to be divided, in removing a bladder and prostate or uterus. Controlled hypotensive anaesthesia has been shown to reduce blood loss in radical cystectomy for bladder cancer. In addition, Ahlering *et al.* also showed that the requirement for blood transfusions was markedly lower in the controlled hypotensive anaesthesia group.[36] Surgeons are constantly looking for new methods of reducing intra-operative blood loss and requirement for blood transfusion in major open surgery. One such method is a new stapling device, Compact Flex Articulating Linear Cutter (Ethicon Endo-Surgery, Cincinnati, Ohio), which showed significant reduction in blood loss and transfusion requirement.[37] Where no reconstruction on the urethral stump is contemplated, haemostasis may be achieved by balloon tamponade of the deep dorsal venous complex (often a major source of bleeding), using a simple large calibre Foley catheter and gentle traction.

Argon beam coagulation can also be used for haemostasis after anterior exenteration, for bladder cancer, as it can for haemostasis following partial nephrectomy.[20]

Partial cystectomy, diverticulectomy, and open bladder stone surgery all present a lower risk in terms of bleeding, but require the usual vigilance and attention to intra-operative haemostasis as would any open or laparoscopic surgical procedure.

Endoscopic procedures

Intractable haemorrhage from the bladder wall during Trans-Urethral Resection of Bladder Tumour (TURBT) is uncommon, but potentially catastrophic. Embolisation of branches of the internal iliac

artery, a minimally invasive technique, has been successfully used perioperatively to control such bleeding.[38] Air insufflation may be used if bleeding obscures vision, as it enables adequate visualisation of the bladder while the blood settles at the bottom of the bladder. Electrovaporisation of bladder TCC can be carried out safely, with minimal risk of perforation and almost no bleeding. A combination of electrosurgical tissue vaporisation and coagulation and electro-vaporisation can achieve the same biological effects as laser treatment, but at considerably lower cost.[39]

Haematuria

Haemorrhage, diffusely from the bladder urothelium can be a difficult problem to tackle, and several methods have been advocated in the past including intravesical instillations of caustic agents, such as, phenol, silver nitrate, or formalin. Intravesical formalin solution has been used to control bleeding due to massive haematuria, in terminal cases of inoperable bladder cancer.[40] Formaldehyde in its natural state is a gas, and the maximum concentration in solution is 37%. A 100% solution of formalin is equivalent to a 37% solution of formaldehyde. This is then diluted to give the required strength. It is instilled under general or spinal anaesthesia and has been used in varying concentrations with different types of follow on solutions. The volume instilled was 10 to 300 ml and contact time was 3 to 30 min. Among the variables the concentration remains the most important, as complication rates increase as the concentration used increases.[41] Fair reported a higher complication rate with 10% formalin and, therefore, advocated using a 1 to 2% solution with a contact time of 10 min. No complications were reported then.[42]

A group in the Netherlands recommended the use of alum irrigation before instituting invasive methods. Alum, an astringent that acts by protein precipitation over the bleeding surface is simple, efficient, less expensive, and non-toxic.[43] Alum as a 1% solution is generally safe and well-tolerated. Local side effects, such as, supra-pubic pain or bladder spasm can be controlled by analgesics and antispasmodics. Haemorrhagic cystitis may also be managed by Argon beam coagulation. This can be used as an alternative to conventional

methods of haemostasis, whenever there is a diffusely bleeding operative site.[20]

Radiation injury to the bladder causes progressive obliterative endarteritis, hypoxic surface damage, ulceration, and bleeding. Hyperbaric oxygen, by causing hyperoxia, reverses radiation induced damage by promoting neo-vascularisation, healthy granulation tissue, and generalised vasoconstriction.[44] Post-radiation haemorrhagic cystitis may be treated with hyperbaric oxygen, which offers a non-invasive therapeutic alternative in patients.[45] Hyperbaric oxygen therapy has been shown to improve angiogenesis and promote healing in radiation injured tissue, including the bladder. It is well-tolerated even in patients debilitated with advanced cancer. Blood loss and long-term remission can be achieved in the majority of patients with haemorrhagic radiation cystitis not responding to other modalities of treatment.[46]

Nd:YAG laser energy has been used for laser coagulation of a bladder haemangioma associated with Klippel-Weber syndrome and causing gross haematuria.[47] Nd:YAG laser coagulation has also been used to successfully treat radiation induced haemorrhagic cystitis. The laser power used was $\leq$ 30 W and pulse duration $\leq$ 3 s.[48]

Prostate

Trans-urethral procedures

Nd:YAG lasers cause coagulation and have been used for trans-urethral laser ablation of the prostate in both the contact and the non-contact modes. In addition to coagulation of the prostatic tissue, adequate haemostasis is achieved as the coagulation extends into the blood vessels as well. The major disadvantages are, however, post-operative irritative voiding symptoms,[49] and delayed unpredictable tissue sloughing. Vaporisation can be carried out with the CO_2 or the Holmium laser. The Holmium laser at a wavelength of 2100 nm has both ablative and haemostatic properties. It has been used in combination with the Nd:YAG laser to resect the prostate gland.[50] The latest in bloodless laser surgery of the prostate is the high power KTP laser.[51] This laser, although expensive, has been reported to have excellent

haemostatic properties. The superficial depth of penetration avoids delayed irritative symptoms that may be seen with other lasers.

Electrosurgical desiccation has also made a comeback in recent times and is a much more affordable energy source than laser. Thick loop resection offers the advantage of improved surgical vision during resection. This enables more accurate and safer resection and slightly improved haemostasis.[52] A variety of modified loop electrodes (thicker, with mini-rollers, oval shape) Trans-Urethral Vapor-Resection of the Prostate (TUVRP), using a vapor resection loop (Wing trade mark; Richard Wolf, Germany) and a Martin ME401® electrosurgical generator (Gebruder Martin, Tuttlingen, Germany), has been suggested in one study as an alternative to standard loop resection. This is due to the reduction in operating time, blood loss, irrigant requirement, nursing contact time, and catheterisation duration offered by the alternative technique. Other advantages include clear vision during surgery and ease of resection.[53] Another study comparing TURP with TUVRP, however, showed no significant difference in blood loss between the two groups, although more patients in the TURP group required blood transfusions.[54]

Super-pulsed radio frequency, a new way of applying electrosurgical energy, has been developed and applied in TURP using a regular thin wire cutting loop. It has been shown to be safe and effective and showed reduced intra-operative and postoperative bleeding. It may be superior to high frequency surgical units or high frequency coagulating intermittent cutting. [55]

A study evaluating the technique, efficacy, and safety of a new electrosurgical modified roller electrode (VaporTrode VE-B; Circon ACMI, USA) showed effective intra-operative haemostasis along with the lack of bleeding or fluid absorption. It also reported the lack of need for high-cost equipment like a laser. This device takes advantage of a combination of electrosurgical cutting and simultaneous electro-desiccation through unique modified electrode design. The electrode (Fig. 5) is mounted on a working element that fits a regular resectoscope and is connected to a high frequency electrosurgical unit with efficient power curve design to achieve the best results. The concentration of high current density at multiple small points of contact with the prostatic tissue on the active electrode surface,

Fig. 5 Resectrode for Trans-Urethral Vaporisation of the Prostate.

leads to a thermal reaction through Ohmic heating. This causes the tissue temperature to rise rapidly until vaporisation occurs. At the same time, low current density areas on the barrel electrode surface provide superficial tissue coagulation and simultaneous haemostasis.[56]

Bipolar trans-urethral prostate electro-surgery resection systems have also been developed to enable longer resection times, with a lower morbidity from irrigant absorption and a lower incidence of TUR syndrome. These come with both loop and roller electrodes and are similar to TURP in that respect. Watch for activated plasma orange glow around the activated loop, during cutting. For coagulation, however, power may need to be slightly reduced depending on the generator design. Flow reduction also helps the superficial coagulation effect. With a double loop system (Vista Controlled Ablation®), one must position centre of the thicker back loop closer to the bleeding vessel and apply gentle downward pressure with both loops into the tissue bed around the bleeding vessel. The coagulation pedal is activated until bleeding stops, keeping loops still. Longer activation time is required than that with monopolar coagulation (Figs. 6 and 7).[57] As yet, there are no randomized controlled trials with these new devices that show reduced blood loss compared to the monopolar equivalents.

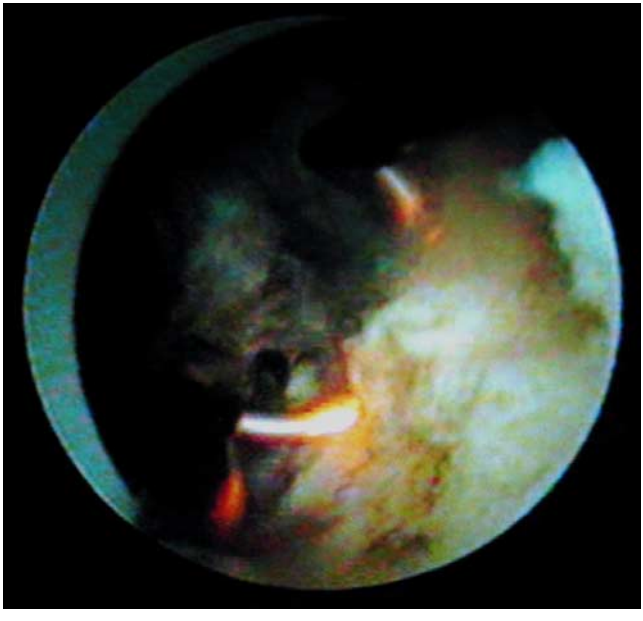

Fig. 6 Bipolar double-loop activated orange glow.

Fig. 7 Vista coblation loop.

Withdrawal of ASA and NSAID one week prior to TURP and prostate biopsies has been recommended to reduce the risk of bleeding.[58] This may, however, be controversial in terms of risk-benefit depending on the indication, and the risk of secondary bleeding is higher probably only in the larger glands.

Preoperative use of Finasteride (a 5α-reductase inhibitor) for three to six months prior to Trans-Urethral Resection of the Prostate

(TURP) has also been shown to reduce intra-operative blood loss and postoperative complications, by one study.[59] Another study suggests that the preoperative use of Finasteride for two weeks could help reduce the bleeding during TURP.[60]

Tranexamic acid is useful in a wide range of haemorrhagic conditions and has been used following trans-urethral prostatic surgery to reduce blood loss and postoperative transfusion requirement. It is more cost-effective and tolerated better than aprotinin.[61]

Open prostate surgery

Open prostatic adenomectomies are still performed in many centres. One study describes a technique for haemostasis, following Freyer's prostatectomy. The technique involves the use of an indwelling catheter with the balloon inflated in the prostatic bed to achieve haemostasis.[62] Phenol injection into the prostate may help reduce the blood loss, and a prospective study done on 100 open prostatectomies concluded that blood loss was minimised in the group that had 5% phenol injected into their prostates, pre-operatively.[63]

Adopting the appropriate position for surgery may help in reducing blood loss. A study evaluating radical retro-pubic prostatectomies showed a decrease in intra-operative blood loss by 80%, when a Trendelenberg position with flexion of the hips was adopted.[64] One of the most important steps in preventing blood loss during radical prostate surgery is the securing of the deep dorsal venous complex. The superficial branch of the deep dorsal vein should be identified and ligated early to prevent accidental tearing of this vessel and subsequent bleeding. A Babcock may be used for *en bloc* bunching of the wide dorsal venous complex,[65] to secure it. These veins can then be controlled with figure-of-eight suture ligatures placed proximally at the bladder neck to reduce back-bleeding[66] and distally near the point of attachment of the pubo-prostatic ligaments. Several technical modifications have been described to control the complex. A modified Babcock clamp has been developed (Munster clamp), which the authors claim significantly reduces haemorrhage during dissection of the deep dorsal veins in radical retro-pubic prostatectomy or cystoprostatectomy.[67] A large needle may also be used to undermine this structure and

facilitate en masse ligation, but this may come off later. It is often better to take smaller bites of tissue with running locking sutures in conjunction with piecemeal division of the complex. After satisfactory ligation has been achieved, transection can be carried out proximal to the ligatures. Any back bleeding may be controlled by temporary tamponade or a few Vicryl running suture ligatures. If the sutures on the complex are inadequate and bleeding does occur, haemostasis may be achieved with additional figure-of-eight sutures.[66] There is a lower risk of bleeding in laparoscopic prostatectomy, due to the venous tamponade provided intra-operatively by the pressure of the pneumoperitoneum. Therefore, patients require less blood transfusion.[68] Studies till date have shown that patient outcomes are similar and there is reduction in postoperative analgesia.

The LigaSure device has also been described for use in radical prostatectomy, for the superficial and the deep dorsal venous complex of the prostate, lateral vascular bundles of the prostate, pelvic lymphatics, and vessels to the seminal vesicles. This study showed shorter operative times and significantly lower blood loss in the group of patients in which LigaSure was used. In addition, there were no instances of haemorrhage or lymphocoele formation, and no transfusions were required.[14] Endoscopic GIA staplers have also been tried for minimising blood loss during radical prostatectomy, and while they did reduce the amount of blood loss, there was an increase in incidence of anastomotic strictures in this group.[69] Finally, a double blind placebo controlled randomised trial done in patients undergoing retro-pubic prostatectomies showed decreased blood loss in the group that received an injection of recombinant factor VIIa in the early operative phase and eliminated the need for transfusion.[70] This Scandanavian study, however, did have rather excessive blood loss in the control group compared with most large series from the USA.

Testis, Epididymis, and Scrotum

The scrotum can pose a problem for postoperative haematomas following hydrocoele surgery, due to the high vascularity of the tunica and its own dependent nature. The ability of the scrotum to stretch, prevents tamponading of the vessels. While it cannot be stressed

enough that there is no substitute for meticulous dissection and haemostasis after dissecting the hydrocoele sac, the incidence of bleeding may be reduced by the postoperative use of a well-fitted scrotal support. If Jaboulay's procedure is performed, the cut edges should be over sewn with locking sutures for haemostasis and, then, tacked posterior to the testis. Lords procedure was described in 1964 as an improvement over existing procedures. It reduces the incidence of haematomas by avoiding excision of the vascular sac of the tunica vaginalis. This procedure consists of using radial sutures to gather the sac around the posterior aspect of the testis and the epididymis. Twenty-two consecutive cases were reported without haematomas.[71] Unfortunately, the disadvantage is a rather bulky feeling testis, afterwards. Various methods have been tried to prevent haematomas, including scrotal suspension using a hypogastric suture, as published by one group.[72]

Penis and Male Urethra

Haemorrhage is potentially a major complication of partial or total penectomy. For partial penectomy, a Penrose tourniquet can be used to reduce blood loss from the penile skin and the subcutaneous tissue. After the incision, the deep dorsal arteries and veins are identified and ligated with 3-0 vicryl sutures then divided. Corporal bodies are dissected, and a vascular non-crushing clamp is placed horizontally across the corporal bodies and transected. The corporal bodies are approximated using a 2-0 vicryl running suture. When the clamp is released, additional bleeding points are ligated using 2-0 vicryl.[73] For total penectomy, although a penrose tourniquet cannot be used, the vascular clamp is used in a similar fashion. The bleeding points are over sewn with 2-0 vicryl. Subcutaneous or skin bleeding vessels are cauterised.[73]

Miscellaneous Laparoscopic Surgery

Bleeding can be a complication of laparoscopic procedures, such as, pelvic node dissection or nephrectomy and is often difficult to manage. Vascular injury can be prevented by use of trocars with

safety devices and use of the Hasson trocar (open technique) to achieve pneumoperitoneum. Laparoscopic clip applicators, including curved endoclips, laparoscopic staplers, laparoscopic suturing, various energy sources (monopolar and bipolar electrocautery, laser, ultrasonic dissectors, and argon beam coagulators), and topical agents (gelatin foam, cellulose, collagen, and fibrin sealant) can be used to achieve haemostasis, although in some cases it may be necessary to convert to laparotomy to stop the bleeding.[74]

Paediatric Urology

Circumcision

Haemorrhage is an important complication of circumcision in children and efforts have been made to try and reduce this. The use of fibrin glue has been advocated and has shown to be helpful even in haemophiliac patients.[4,75,76] The use of bipolar diathermy has been successfully used in the paediatric age group for "bloodless circumcisions".[77] Ultrasound dissection scalpels can be used, as they combine gentle tissue dissection with simultaneous haemostasis without the fear of the risks of electrocautery.[78] Neonatal circumcisions are often performed with a variety of devices, such as, the Plastibell, the Gomco clamp, and the Mogen clamp.[79,80] The Mogen clamp has been reported to cause virtually no blood loss.[80] A technique has been described using the Plastibell as a template. The appropriate size of device is chosen and applied to the glans. The foreskin is then pulled back over the bell, and a ligature is tied around the groove. Excess skin is removed with the cutting electrocautery, and the edges are approximated with 5.0 chromic sutures. This technique has shown to be more effective in achieving haemostasis than sleeve circumcision.[81]

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Haemostasis in Obstetrics and Gynaecology: Modern Management and Methods

Deirdre Lyons

The principles of haemostasis in Obstetrics and Gynaecology are similar to those in other surgical specialties. The uterus and the endometrium, however, have some unique properties, especially in terms of menstruation, pregnancy, and delivery.

The myometrial smooth muscle cells are not homogenous. They are embedded in extracellular material composed mainly of collagen fibres, which facilitates the transmission of contractile forces generated by individual muscle cells.[1] The muscle cells communicate with each other through gap junctions. These junctions are believed to synchronise myometrial function by conduction of electrophysiological stimuli during labour. In both human and animal myometria in late pregnancy, the gap junctions increase in number until onset of labour. The formation of gap junctions has been studied *in vitro*, and

the regulatory roles for oestrogen, progesterone, and prostaglandins have been established. The relationship between the electrical activity, the conductivity properties of the myometrium and the density of gap junctions has been shown. This indicates that the various related components of myometrial cellular regulation including the formation of gap junctions, enhancement of electrical activity, and response to oestrogen, oxytocin, and prostaglandins are simultaneous events. These collectively contribute to the increased myometrial activity of labour and postpartum.

The effect of oxytocin is mediated through myometrial oxytocin receptors that are modulated by various factors. Following administration of oestrogens the number of uterine receptors sensitive to oxytocin and α-adrenergic agonists increases. This can be prevented by concurrent administration of progesterone. In binding to the receptor, oxytocin has been shown to inhibit the Ca^{++} ATPase of the myometrial cell membrane. This pumps Ca^{++} from the inside to the extracellular milieu and promotes the influx of Ca^{++} both from the sarcoplasmic reticulum and the extracellular area. The increase in concentration of cytoplasmic Ca^{++} activates the contractile process. Oxytocin may also have a central regulatory function. At term, the deciduas parietalis shows a high concentration of oxytocin receptors. This may be a stimulus for prostaglandin synthesis as prostaglandins are found in high concentrations in decidual tissue obtained from women in labour.

Progesterone effects on the myometrium are characterised by a relative quiescence and uncoupling of the excitation–contraction mechanisms.

Oestrogens stimulate or increase sensibility to α-adrenergic receptors, leading to increased production of Prostaglandin F2A. In contrast, progesterone stimulates β-adrenergic receptors, leading to preponderance of prostacyclin (PGI2) and, via C AMP, to the relaxation of smooth muscle. Mifepristone, a steroid acting as antiprogesterone at the receptor level, results in increased uterine activity and increased sensitivity to prostaglandins.

Prostaglandins are components of the eicosanoid system. They are acidic lipids arising from the principal precursor, arachidonic acid, via three different pathways. This is catalysed by cyclooxygenase

leading to prostaglandins, prostacyclin, and thromboxane and by lipoxygenase leading to leucotrienes. Human amnion and chorion mainly produce PGE2 and PGF2A. It is suggested that the synthesis of PGE2 is the key event in the onset of regular contractions. Prostaglandins also cause increased myometrial contractility, and there appears to be a regional sensitivity of the uterus to various prostaglandins.

In contrast to other hormones, prostaglandins are synthesised at the site of action. PGE2 and PGF2A are known to stimulate uterine contractility, most likely acting as Ca^{++} ionophores.

The action of prostaglandins appears to be mediated by specific receptors located on the plasma membranes of target cells. The increase in myometrial activity is directly related to the rise in PGE2 and PGF2A. Prostaglandins produced in the placenta probably play a major role in the mechanism of placental separation and expulsion.

The rapid metabolism of natural prostaglandins is the reason why a number of analogues have been developed, that are not substrates for the initial step of the enzymatic degradation by 15-OH-dehydrogenase. These derivatives are more potent than the parent compound and action is more prolonged and more specific on uterine rather than other smooth muscle tissue.

The subcellular structure of smooth muscle is different from striated muscle. In smooth muscle cells, the thick myosin and the thin actin filaments occur in long random bundles throughout the smooth muscle cells and the continuity of the filaments is not interrupted by Z lines. Instead, intermediate filaments form a network that links protein structures known as dense bodies. They link the individual fibrils, composed of actin and myosin, into integrated mechanical units. Smooth muscle can exert pulling forces in any direction due to its organisation. This enables the uterus to generate forces in any axis necessary and assume any shape to accommodate foetuses of various sizes, during labour.

The endometrium is composed of two layers, the upper functional layer that is shed at the time of menstruation and an underlying basal layer from which the endometrium regenerates after each menstrual shedding. The endometrium shows the presence of oestrogen, progesterone, and androgen receptors in the stroma.[2]

Haemostatic mechanisms have two functions:

(a) To confine the circulatory blood to the vascular system.
(b) To arrest bleeding from injured vessels.

These mechanisms depend on:

(i) Normal vasculature.
(ii) Platelets — number and function.
(iii) Coagulation factors.
(iv) Healthy fibrinolysis.[3]

VASCULAR INTEGRITY

It is thought that platelets have a major role in maintaining vascular integrity as in conditions where their number and function is abnormal, widespread capillary haemorrhages occur. In health, platelets are constantly sealing microdefects. Minifibrin clots are formed, and the fibrin is then removed by the fibrinolytic system. Prostacyclin (PGI2) is an unstable compound, first discovered in 1976. It is the principal prostanoid synthesised by blood vessels and is a potent vasodilator and inhibitor of platelet aggregation. It is proposed that there is a balance between prostacyclin and thromboxane A2 — a powerful vasoconstrictor and platelet aggregating agent. Prostacyclin prevents aggregation at much lower concentrations than is needed to prevent adhesion. Therefore, vascular damage leads to platelet adhesion, but not necessarily platelet aggregation and thrombus formation. If injury is small, small platelet thrombi form and are washed away by the circulation. The extent of the injury is, however, an important determinant of the size of the thrombus and whether or not platelet aggregation is stimulated. PGI2 syntethase is abundant in the intima and progressively decreases from the intima to the adventitia. It follows that severe vessel damage or physical detachment of the endothelium will lead to development of a large thrombus rather than simple platelet adherence.

An essential function of the haemostatic system is rapid reaction to injury, which remains confined to the area of damage. Control mechanisms are required to stimulate coagulation after trauma and

limit the extent of the response. The substances involved in the formation of the haemostatic plug normally circulate in inert form until activated at the site of injury or by some factor released in the circulation that will trigger off intravascular coagulation.

LOCAL RESPONSE

Platelets adhere to collagen on the injured basement membrane. This initiates a series of changes in the platelets themselves, including a change in shape and release of ADP and other substances. ADP release stimulates further platelet aggregation. The coagulation cascade is triggered off, and the action of thrombin leads to the formation of fibrin, which converts the loose platelet plug into a firm, stable wound seal. The role of platelets is less important in large vessel injury because platelet aggregates are of insufficient strength and size to seal the defect. The coagulation system along with vascular contraction is important here.

COAGULATION SYSTEM

The coagulation system results in the formation of insoluble fibrin clot from the soluble precursor, fibrinogen, found in plasma. The coagulation cascade is a complex interaction of clotting factors and sequential activation of a series of proenzymes. There are two mechanisms, the intrinsic mechanism that involves the activation of Factor XII by collagen after blood vessel injury and the extrinsic mechanism that involves activation of Factor VII by thromboplastin release from damaged tissue. Both mechanisms are required for normal haemostasis. These two pathways interact and share a common pathway after activation of Factor X.

The intrinsic mechanism proceeds spontaneously and is slow. It requires 5 to 20 minutes for visible fibrin formation. A specific lipoprotein, Thromboplastin, is contained in all tissues and accelerates the rate at which blood clots. The placenta as well as the lung and the brain are particularly rich in tissue factor, which will produce fibrin formation in 12 seconds. This acceleration of coagulation is

brought about by bypassing the reactions involved in the intrinsic system.

Powerful control mechanisms must act to prevent dissemination of coagulation beyond the site of trauma. The action of thrombin *in vivo* is controlled by its absorption into the locally formed fibrin and by the presence of a potent inhibitor, anti-thrombin III, an α2-globulin, which destroys thrombin activity.

Normal pregnancy is accompanied by major changes in the coagulation system with increases in levels of Factors VII, VIII, and X and, particularly, a marked increase in the level of plasma fibrinogen. The effects of pregnancy on the coagulation system can be seen as early as the third month of pregnancy. In late pregnancy, the level of fibrinogen is at least double that of the non-pregnant state.

FIBRINOLYSIS

This is an essential part of the interacting dynamic mechanism and is dependent on plasminogen activator in the blood. Fibrin is digested by plasmin, a proenzyme derived from an inactive plasma precursor, plasminogen. Activator levels are increased after surgical operations, trauma, and strenuous exercise.

Tissue activator is especially rich in the uterus and the ovaries, but cannot be extracted from the placenta. Activity around veins is greater than around arteries.

There are two inhibitors of fibrinolytic activity, anti-activators (anti-plasminogens) and anti-plasmins.

Anti-plasminogens include e-aminocaproic acid (EACA) and tranexamic acid. Tranexamic acid in a dose of 500 mg to 1 g gds is used in the control of menorrhagia, often as a first line treatment.[4]

Fibrin degradation products are formed when fibrinogen or fibrin is broken down by plasmin. Plasma fibrinolytic activity is decreased during pregnancy and returns to normal within one hour after placental delivery. The fact that fibrinolytic activity resumes rapidly following delivery of the placenta and the placenta has been shown to contain inhibitors of fibrinolysis suggests that inhibition of fibrinolysis during pregnancy is mediated through the placenta.

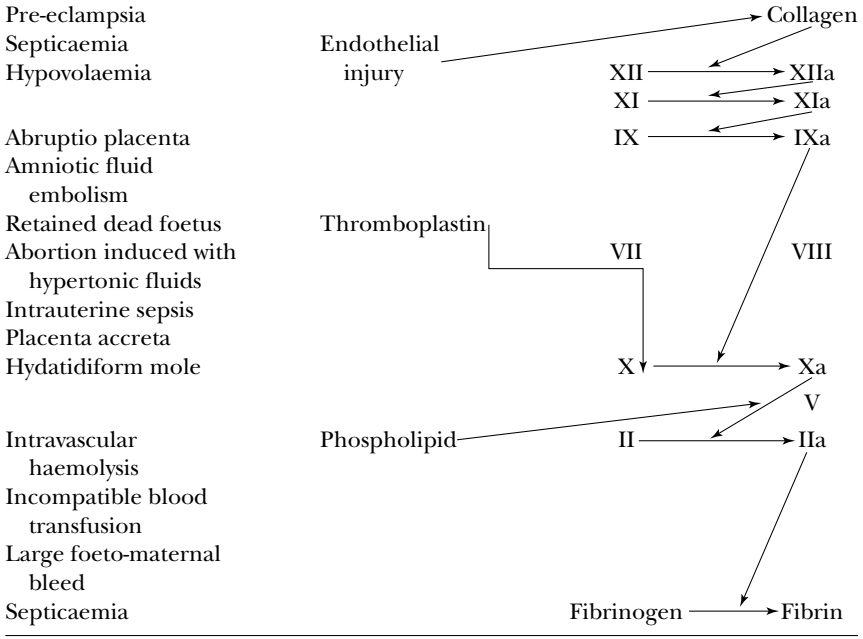
Overall, the changes in the coagulation system during normal pregnancy are consistent with a continuous, low-grade level of coagulant activity. Fibrin deposition can be demonstrated in the intervillous space of the placenta and in all the walls of the spiral arteries supplying the placenta. The elastic lamina and the smooth muscle of these spiral arteries are replaced by a matrix containing fibrin, as pregnancy progresses. This allows expansion of the lumen to accommodate increasing blood flow and reduces arterial blood pressure flowing to the placenta.

Normal pregnancy is associated with an increase in cardiac output from 4.5 L to 6 L. After placental separation (third stage of labour), blood supply ranging between 500 and 800 ml/min to the uterus, has to be arrested within seconds to prevent a serious haemorrhage. Myometrial contraction plays a vital role in securing haemostasis, by reducing the blood flow to the placental site. Rapid closure of the terminal part of the spiral arteries will be further facilitated by the structural changes in their walls. The placental site is rapidly covered by a fibrin mesh following delivery. The increased levels of fibrinogen and other coagulation factors will meet the sudden demand for haemostatic components, following placental separation.

DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC)

Changes in the haemostatic system during pregnancy and the local activation of the clotting system at parturition carry a risk not only of thromboembolism, but also of DIC, consumption of clotting factors and platelets, leading to severe bleeding. One of the problems with DIC is its definition. It is always secondary to some general stimulation of the coagulation system. Table 1 shows the DIC trigger mechanisms. DIC is manifested in several forms, from a compensated state with no clinical manifestations, but evidence of increased production and breakdown of coagulation factors to the condition of massive uncontrollable haemorrhage with very low levels of plasma fibrinogen, raised levels of fibrin degradation products (FDPs), and variable degrees of thrombocytopaenia. Fibrinolysis is stimulated by DIC, and

Table 1. Trigger Mechanisms for DIC in Pregnancy



FDPs resulting from the process interfere with the formation of firm fibrin clots. A vicious cycle is established, leading to further bleeding.

OBSTETRICS

Despite advances in obstetric care and improved blood transfusion, haemorrhage is still a major cause of maternal morbidity and mortality. The Confidential Enquiry into Maternal Deaths 1997–1999 showed seven maternal deaths related directly to haemorrhage and seven other deaths where haemorrhage was a significant cause. It has been reported that death from haemorrhage occurs in 3.3 per million maternities.[5] Deaths from postpartum haemorrhage (PPH) account for 17 to 40% of the maternal mortality in the developing world. For women who refuse blood transfusion, the risk of death from PPH is one in 1000, similar to that in developing countries. Morbidity is also associated with obstetric haemorrhage and studies suggest that severe, life-threatening haemorrhage may occur in 6.7 per 1000 deliveries.[6,7]

A recent study published in the *British Journal of Obstetrics and Gynaecology*, in April this year,[8] suggests a severe maternal morbidity rate of 3.8 per 1000 maternities, with major obstetric haemorrhage accounting for 50% of events. It defines 13 categories of severe maternal morbidity and demonstrates that it is possible to quantify maternal morbidity on a national basis. The study also suggests that a national reporting system for maternal morbidity should be set up. This is dependent on a local risk management system being in place in every unit, as recommended in "A First Class Service: Quality in the new NHS".[9]

Congenital coagulopathies in women are not common, but are associated with obstetric haemorrhage. The most common congenital coagulopathies are von Willebrand's disease, haemophilia A, and haemophilia B (Christmas disease). von Willebrand's disease constitutes a heterogenous group of haemorrhagic disorders that are usually transmitted as autosomal dominant traits, although autosomal recessive transmission of some variant types occurs.[10] The prevalence of von Willebrand's disease is at least 3 to 4 per 100,000 in the UK and due to its autosomal pattern of inheritance is the commonest congenital coagulopathy affecting women. There is an elevation in factor VIII: v WF during pregnancy or oral contraceptive use. The von Willebrand's factor acts as a carrier and stabiliser of factor VIIIc, preventing it from inactivation or catabolism. Deficiency in v WF results in defective platelet-endothelial and platelet–platelet interactions. Haemophilia A and B are X-linked recessive disorders and among carrier women only about 1 in 10 has excessive bleeding.

Cryoprecipitate has been the treatment of choice for severe bleeding episodes and surgical procedures in von Willebrand's disease. It was thought to be preferable to high potency factor VIII concentrates, which do not elevate ristocetin co-factors as effectively as cryoprecipitate. There is, however, considerable variability in the correction of bleeding times with cryoprecipitate and even laboratory assessment of v WF activity (ristocetin co-factor) does not predict reliably the clinical response. These patients are now generally covered in labour by an alternative to blood products, desmopressin, a synthetic analogue of anti-diuretic hormone. This treatment releases endogenous factor VIII: v WF from vascular epithelium and is used

for **both** prophylaxis and treatment of bleeding. In the management of pregnant women it is important to establish the type and monitor haemostatic variables, especially during the third trimester.

Postpartum Haemorrhage

Postpartum haemorrhage (PPH) is a major cause of maternal mortality, worldwide. Average blood loss during delivery increases with the complexity of delivery mode. Traditionally, primary PPH is defined as blood loss of 500 ml or more from the genital tract within the first 24 hours of delivery.[11] This has been challenged recently as blood loss measurement is inaccurate. Major obstetric haemorrhage is defined as blood loss of greater than 1000 ml, about 1.3% in the UK.[12] Another definition suggests excessive blood loss is marked by a 10% drop in haematocrit or by the need for red cell transfusion. PPH can be divided into primary (within first 24 hours of delivery) and secondary (between 24 hours and 6 weeks post-delivery). Secondary PPH is generally thought to be due to infection.

The aetiology of primary or early PPH is as follows:

- Uterine atony.
- Retained placental fragments.
- Lower genital tract lacerations.
- Uterine rupture.
- Uterine inversion.
- Placenta accreta.
- Hereditary coagulopathy.

Uterine atony complicates one in 20 deliveries, resulting in excessive blood loss when adequate myometrial contraction fails to occur after placental expulsion. Risk factors include conditions where the uterus is overdistended (polyhydramnios, multiple gestation, and foetal macrosomia) or fatigued (rapid or prolonged labour and chorioamnionitis). Antepartum haemorrhage is also a risk factor, but contrary to popular opinion, grand multiparity has not been found to be a risk factor.[13]

The first step in managing PPH is appreciating its severity and evaluating its primary cause. Appropriate senior help should be sought

and each unit should have a PPH protocol that is activated at the time of major obstetric haemorrhage. This should include a dedicated bleep via hospital switchboard, involving all appropriate personnel including obstetricians, anaesthetists, and haematologists (both medical and laboratory staff). Guidelines should be readily available on labour ward and staff education should be undertaken in the form of practice drills. One study showed a significant reduction in the incidence of massive postpartum haemorrhage from 1.7 to 0.45% after dissemination of guidelines and commencement of practice drills.[14]

There has been some work on the use of the thromboelastograph (TEG) in the assessment and management of major haemorrhage.[15]

The thromboelastogram is an *in vitro* monitor of the viscoelastic properties of blood. It has never been popular with haematology laboratories as it is not capable of performing multiple batch analysis. TEG detects increasing stickiness as fluid blood becomes clot. The trace monitors the entire process of coagulation and provides information on the rate and the strength of clot formation and its subsequent decay. TEG is capable of making a decision between dilutional coagulopathy and DIC. Therefore, it may be a useful tool in deciding management of patients from a blood product point of view.

Uterine atony, the most common aetiology, is diagnosed by bimanual palpation and initially managed by uterine massage and by administration of intravenous oxytocin. When carrying out bimanual uterine compression, the hand in the vagina should elevate the uterus to keep the uterine arteries on stretch. Active management of third stage of labour helps prevent PPH, and routine administration of an oxytocic reduces the risk of PPH by 40%.[16] Syntocinon is a synthetic nonapeptide that is routinely administered as a first line agent. It is given as an I.V. bolus (10 iu) or an infusion of 40 units at a rate titrated to control the uterine atony. Ergometrine, an ergot alkaloid can also be used, but not in patients with hypertension as there is a great risk of severe hypertension and myocardial ischaemia.

Prostaglandins are important in the treatment of PPH. The next step is usually to give intramuscular Carboprost, which is 15-methyl prostaglandin F2. This is administered in a dose of 250 μg intramuscularly (skeletal or intramyometrial) every 15 minutes, if necessary, up to a maximum of 2 mg. Intramyometrial carboprost is faster

and more effective[17] and although not licensed for use in this way can be used in individual cases under direct consultant supervision in severe atonic PPH. Misoprostol is a synthetic prostaglandin E1 analogue marketed for the prevention of gastric ulcers. Misoprostol has been extensively studied for the purpose of preventing PPH,[18,19] and an oral dose of 200 to 400 μg has the equivalent uterotonic effect on the uterus as intramuscular syntometrine.[20] Misoprostol in a dose of 1000 μg, given rectally to PPH cases unresponsive to oxytocin and ergometrine, showed control of haemorrhage in three minutes in all 14 cases.[21] Detectable misoprostol can be found in the blood just two minutes after oral misoprostol administration. Misoprostol is an oral dose and is stable at room temperature. It has a long shelf life, which would be a major advantage in its use in the developing world.

There are recently published articles on the use of recombinant factor VIIa for treatment of massive obstetric haemorrhage. Recombinant factor VIIa is a vitamin K-dependent protein used in the treatment of individuals with Haemophilia A and B inhibitors, acquired inhibitors, and congenital factor VII deficiency.

Specifically, recombinant factor VIIa complexes to tissue factor and, therefore, promotes the activation of factor X to Xa and activation of factor IX to Ixa. It also promotes generation of thrombin. The rate of thrombin formation is enhanced, leading to a full thrombin burst. This is necessary for providing a fully stabilised fibrin plug with a tight fibrin structure, making it resistant to premature lysis.[22] There are also platelet-dependent clotting mechanisms mediated by recombinant factor VIIa that do not need the participation of tissue factor.[23] The reports are dramatic, with arrest of severe haemorrhage in 10 minutes. Adverse effects occur infrequently (1%) and include thrombosis and myocardial infarction. The main drawbacks are cost, although possibly decrease in ITU stays and less operative intervention may make it cost effective. The half life is also short at two hours and repeated doses may be required.[24]

Surgical Treatment

If all forms of medical treatment have been undertaken and have failed, then surgical intervention becomes necessary. The patient

should be adequately resuscitated as much as possible, and blood and FFP and cryoprecipitate should be given as required to correct DIC.

If the uterus appears contracted, but bleeding is still heavy early recourse to theatre to ensure the cavity is empty and suture any vaginal or cervical lacerations is advocated. This should be undertaken in a theatre setting with adequate light and assistance. If these methods fail, it is worth considering the use of a hydrostatic balloon. The Rusch balloon, which was previously used in Urology for bladder stretching, can be used. Through its drainage port, up to 500 ml of normal saline can be inserted into the catheter balloon, which is inserted into the uterus. A Sengstaken–Blakemore tube can also be used to blow up the stomach balloon, but it is complex to use and expensive.[25] The catheter is usually left *in situ* for 24 hours, while uterine contractions are maintained with Syntocinon. The advantage of the balloon is it prevents the patient from having a laparotomy.[26] Another option to create tamponade within the uterus is to pack the uterus.[27] Uterine packing can be considered for control of haemorrhage secondary to uterine atony, placenta accrete, and placenta praevia. The instrument used in the referenced paper was a Torpin packer, but the most important issue is to pack the uterine cavity completely and uniformly. The incidence of concealed haemorrhage and infection do not seem to be major problems as long as the patient is covered with systemic antibiotics. The pack is generally removed after 5 to 96 hours.

If uterine atony is unresponsive to the previous measures, then a B-Lynch brace suture can be placed.[28] This is undertaken as follows:

(1) The patient is usually under anaesthesia and should have already been catheterised as part of the PPH protocol.
(2) The abdomen is opened by an appropriate Pfannenstiel incision, or if the patient has had a caesarean section the scar should be re-opened.
(3) On entering the abdomen a lower segment incision is made after dissecting off the bladder, and the cavity is evacuated, examined, and swabbed out.
(4) The uterus is exteriorised, and this puts the uterine arteries on stretch. Bimanual compression is commenced to assess the potential success of the suture.

(5) A large needle (B-Lynch used 2 chromic catgut) 1 vicryl suture is used. This punctures the uterus 3 cm from the lower border of the uterine incision and 3 cm from the lateral border. The suture is threaded through the uterine cavity to emerge at the upper incision 3 cm above and, approximately, 4 cm from the lateral border.
(6) The suture, now visible, is passed over to compress the uterine fundus approximately 3 to 4 cm from the ipsilateral corneal border.
(7) The suture is fed posteriorly and vertically to enter the posterior wall of the uterine cavity at the same level as the upper anterior entry point.
(8) The suture is pulled under moderate tension, assisted by manual compression exerted by the first assistant. The length of suture is passed back posteriorly through the same surface marking as on the right side, the suture lying horizontally.
(9) The suture is fed posteriorly and vertically over the fundus to lie anteriorly and vertically, compressing the fundus on that side. The needle is passed in the same fashion on that side through the uterine cavity and out approximately 3 cm anteriorly and below the lower incision margin on the left side.
(10) The two lengths are pulled taut, assisted by bi-manual compression, to minimise trauma and to achieve or aid compression. During this compression, the vagina is checked to see if bleeding is controlled.
(11) The uterus is compressed by an experienced assistant, and the principal surgeon throws a double throw knot followed by 2 to 3 further throws to ensure tension.
(12) The lower transverse incision is closed in the normal way.
(13) For a major placenta praevia they suggest that an independent figure of eight suture be placed at the beginning, anteriorly or posteriorly or both, prior to the application of the B-Lynch suture.

In the original report there were two further pregnancies suggesting this suture does not compromise the uterus. Danso and Reginald reported using a combined B-Lynch suture with intrauterine balloon

and suggested that this combination may work well together when one or the other procedure may not work on their own.[29]

Uterine artery ligation was shown to be successful in 255 patients, with only 10 patients over a 30-year period. The technique involved placing a suture to include 2 to 3 cm of the myometrium at a level of 2 to 3 cm below the uterine incision. Uterine viability is maintained via collateral circulation.[30] Stepwise uterine devascularisation has been described in a report from Egypt. The steps involved are:

(1) Unilateral uterine artery occlusion.
(2) Bilateral uterine artery ligation (at the upper part of the lower uterine segment).
(3) Lower uterine artery ligation after mobilisation of the bladder.
(4) Unilateral ovarian vessel ligation.
(5) Bilateral ovarian vessel ligation.

Myometrium was included in the ligatures of (1) to (3). Steps (1) and (2) were deemed to be successful in 80% of cases.[31] Internal iliac artery ligation appears to control blood loss by reducing arterial pulse pressure, essentially converting the pelvic arterial system into a venous one. In one study, arterial pulse pressure was reduced 14% by contralateral, 77% by homolateral, and 85% by bilateral internal iliac artery ligation.[32] The procedure is technically challenging and should only be undertaken with the supervision of an experienced pelvic surgeon or vascular surgeon. It is successful only in about 42% of cases.

Selective Arterial Embolisation, in a literature review in 1997,[33] showed a high success rate of selective artrial embolisation for postpartum haemorrhage. Potential complications include haematoma formation (at catheter placement site), infectious complications, and ischaemic phenomena. In addition, this is not available in all centres due to lack of equipment and interventional radiologists.

Hysterectomy was performed as an emergency, in one study, for uterine atony (in 43% of cases), placenta accreta (30%), uterine rupture (13%), low transverse incision extension (10%), and leiomyomata (4%).[34] These can be subtotal or total, the most common for total abdominal hysterectomy was placenta accreta (81%) and subtotal hysterectomy was uterine atony (64%).[35]

In patients who refuse blood transfusion and where there is access to the technology, autotransfusion can be undertaken.[36] One study did not show evidence of infection or amniotic fluid embolism.

Placenta accreta is becoming a more prominent cause of PPH in recent years, probably due to the increase in caesarean section. The incidence of placenta accreta in an unscarred uterus was 0.26%, increasing linearly to 10% in patients with four or more caesareans. Patients with placenta praevia and an unscarred uterus have 5% risk of clinical placenta accreta. This rises to 65% if there is a placenta praevia and four or more caesareans.[37] Patients with suspected placenta accreta should be delivered electively, preferably before labour starts and prior to serious vaginal bleeding. Some authors have suggested delivery at 35 weeks with prior consideration of amniocentesis, to assess foetal lung maturity. Most units would deliver at about 37 weeks in a well-equipped theatre with adequate numbers of senior staff available and full blood bank and haematology support. General anaesthesia should be considered as these procedures can be prolonged. In cases where serious bleeding is anticipated intra-operative autotransfusion, intra-arterial catheters (for balloon occlusion), selective arterial embolisation, and other modalities should be considered prior to delivery. Adequate operative field access cannot be over-emphasised and, generally, a midline incision is performed. If a decision to perform hysterectomy is taken due to morbid adherence of the placenta, then the placenta is left *in situ* after delivery of the baby. The uterine incision is closed, and the hysterectomy proceeds. The placenta is always left *in situ* after delivery of a foetus of an abdominal pregnancy as to attempt to remove a placenta that may be embedded in one of the pelvic vessels, can cause catastrophic haemorrhage leading to death. The placenta is generally left *in situ* to reabsorb itself over some weeks to months, or administration of methotrexate can be considered.

Bleeding can continue after hysterectomy, often due to an underlying coagulopathy and the use of intra-abdominal[38] or pelvic pressure pack.[36] The pelvic pressure pack can be made from an X-ray cassette bag. It can be filled with gauze rolls and tied end to end. This will provide enough volume to fill the pelvis. The pack is introduced abdominally with the stalk exiting the vulva. Mild traction is exerted

by tying a litre bag of fluid to the stalk and hanging it over the end of the bed.

To summarise, obstetric haemorrhage is frightening. Awareness and rapid assessment of haemorrhage and instituting measures to decrease bleeding can, however, reduce the morbidity and the mortality from haemorrhage.

GYNAECOLOGY

Menorrhagia is the most common problem that is presented before general practitioners and at gynaecology clinics. It causes considerable discomfort, anxiety, and disruption in women's lives. The definition of menorrhagia is blood loss of greater than 80 ml during menstruation. It is difficult to assess this objectively but a simple measure using a pictorial chart may be useful.[39] Menorrhagia is experienced by 30% of women in the reproductive age,[40] and accounts for 60% of general practitioner consultations for menstrual disorders. Menorrhagia accounts for 12% of gynaecology referrals and is the most common cause of iron deficiency anaemia in pre-menopausal women. Fifty percent of women will not have a cause for their menorrhagia, and this is called dysfunctional uterine bleeding. Other causes of menorrhagia are fibroids, polyps, endometrial hyperplasia, endometrial carcinoma, and congenital coagulopathies. Uterine arteriovenous malformation is also a cause, but occurs very rarely.

The endometrium is a target tissue for steroid hormones and is composed of two layers. The upper functional layer is shed at the time of menstruation and the endometrium regenerates after menstrual shedding from the basal layer. Oestrogen is the steroid responsible for proliferative changes during the follicular phase, and exposure to progesterone results in differentiation during the luteal phase.[2] Oestrogen and progesterone receptors are upregulated in the proliferative phase. The upregulation occurs in both glandular and stromal tissues. In the secretory phase, a downregulation of oestrogen receptors is noted in both glands and stroma. Progesterone receptors are also downregulated in the glands, but their expression persists in stromal tissues.[41]

It is recommended that general practitioners offer women at least one course of drug therapy before referring them for surgery.[4] Many drug therapies are of uncertain effectiveness and patient compliance can be poor. The use of non-hormonal drugs, for example, tranexamic acid and the NSAID, mefenamic acid can result in fewer referrals and surgical procedures.[42] The most commonly prescribed drug is progestogen, but it is ineffective in the normally used doses.[43] Its effectiveness may, however, improve at higher doses.[44]

A meta-analysis and survey of prescribing habits of general practitioners showed tranexamic acid was the most effective treatment for menorrhagia, reducing blood flow by nearly 50%. It was, however, used in that survey by only 1.3% of general practitioners. Mefenamic acid can also be effective in reducing blood flow by 30%.[45]

A hysteroscopy and curettage is not a treatment for menorrhagia and is only a diagnostic tool.

The levonorgestrel-releasing intrauterine system (LNG-IUS) comprises a T-shaped plastic frame with a cylinder of the synthetic progestin, levonorgestrel enclosed in a silastic sleeve. This permits slow and controlled release of 20 μg of levonorgestrel into the uterine cavity over 24 hours.[46] In the aforementioned trial Irvine *et al.* found decreased blood flow by 94% at three months. They also found increased patient satisfaction with LNG-IUS and higher continuation with treatment (80% continuation with LNG-IUS as opposed to 20% with oral progestogens). The LNG-IUS induces marked decidualisation of the endometrium. There is also a reduction of the secretory activity of the epithelial glands and in cellular proliferative activity. Cyclical activity of the endometrium is rapidly lost, and features of atrophy and decidualisation are evident within one month of insertion.[2] The LNG-IUS produces a greater reduction in menstrual blood loss than non-steroidal anti-inflammatory drugs, progestogens or tranexamic acid. In one study, 66% of women treated with LNG-IUS became either oligoamenorrhoeic or amenorrhoeic after 12 months.[47]

A randomised, controlled trial comparing LNG-IUS and hysterectomy showed LNG-IUS was as effective as hysterectomy for outcomes of quality of life and psychological well-being, and it was cost-effective

at one year.[48] There is also evidence to suggest a reduction in the incidence and the size of fibroids in patients using LNG-IUS.[49]

The uterine thermal balloon reported a success rate of 88–91% at one year follow-up in one study.[50] This consists of a 16 cm by 4.5 mm diameter catheter with a latex balloon at its distal end housing a heating element. The controller unit continuously monitors, displays, and controls pre-set intra-balloon pressure, temperature, and treatment duration. The balloon was checked before insertion and filled with a variable volume of 5% dextrose until a mean starting pressure of 167 +/− 8 mmHg was achieved. The treatment cycle commenced when the fluid temperature reached 87 +/−5 °C and continued for 8 minutes. At the conclusion of the treatment the balloon was emptied and removed. Then, it was checked for leaks.

The success rates at three and six months were higher in patients with smaller cavities and higher balloon pressures. In the above study, women who received one or two doses of gonadotrophin releasing hormone analogues (GnRH) pre-treatment with thermal balloon therapy had statistically higher rates of amenorrhoea and spotting. This may have been the result of thinning the endometrium and decreasing blood flow. The procedure is fairly risk-free and is easy to learn.

The microwave endometrial ablation system (MEA) is a third generation thermal ablation device designed to ablate the endometrial lining of the uterus. This procedure is at least as effective as endometrial resection and rollerball ablation. It can also follow the contours of the uterine cavity and can effectively treat all areas of the uterine cavity regardless of shape, including cavity lengths of 6 to 14 cm and those with fibroids </= 3 cm and polyps. Low levels of microwave energy are used to vigorously vibrate water molecules in tissue to quickly and effectively heat the lining of the uterus. The total depth of tissue destruction is 5 to 6 mm. The success rates are 96% significant reduction in menstrual blood flow and 61% amenorrhoea at 12 months.[51]

The removal of the endometrium has interested gynaecologists for many years. The removal can be successful only if the full thickness of the endometrium and the superficial myometrium, including the

deep basal glands that are believed to be the primary foci for endometrial regrowth, are removed. This is because the endometrium has excellent powers of regeneration. The endometrium may be removed under direct hysteroscopic vision using an electrosurgical loop or by ablating the endometrium with some form of thermal energy. Goldrath *et al.* described the first hysteroscopic endometrial ablation using neodymium:yttrium:garnet (Nd:YAG) laser photovapourisation, and good control of bleeding was obtained in 21 out of 22 women. The risk of hysterectomy after laser ablation was 15% in another study[52] over five years, with no cases of perforation in over 1000 cases studied. The ELITT (endometrial laser intrauterine thermotherapy) uses diode laser light energy combined with interstitial thermo-therapy fibre technology. This system requires neither intensive training nor hysteroscopic control. It poses less risk as power per unit area is 1/1000 times lower. The 830 nm wavelength laser-light penetrates the uterine wall to a precise depth and is absorbed by the haemoglobin. This absorbed light is then transformed into heat, warming the endometrium and causing controlled coagulation.[53] The inherent light-scattering inside the endometrium contributes positively to the uniformity of laser-light distribution and the resultant coagulation. The success rates at one year were 71% amenorrhoea and 91% hypomenorrhoea. Eighty-seven percent patients were "very satisfied" with the procedure.

In the US, Vaincaillie described the Rollerball endometrial ablation. This procedure produces sufficient thermal necrosis of the endometrium and superficial myometrium using simple and cheap electrosurgical equipment. Satisfaction rates are comparable to the other commonly used hysteroscopic techniques. Endometrial resection in long-term trials[54] reported reduction of menstrual flow and good clinical outcomes. Cooper *et al.*[55] showed that women were generally more satisfied with resection than medical treatment (76 versus 27%). Haemoglobin levels were significantly increased only following transcervical resection. The safety profile of these techniques was assessed in the MISTLETOE study[56] suggested that laser and rollerball ablations are associated with the least operative and postoperative complications. The loop resection group was the only group to show a relationship between operator experience and complications.

Uterine artery embolisation is mainly employed in the treatment of fibroids and causes a statistically significant reduction of up to 85% in objectively measured blood loss. There also appeared to be a 40%[57] to 74%[58] reduction in uterine volume and even though the uterus may remain large symptoms may still be improved.[59] Complications include ovarian failure causing amenorrhoea in 7 to 14% patients, therefore, counselling is important prior to undertaking this procedure. Infective complications of approximately 1% and progression to hysterectomy due to dissatisfaction with the procedure about 3%.

There is a newer technique using MRI guided percutaneous laser ablation of uterine fibroids and recently magnetic resonance focused ultrasound to decrease the fibroid volume and improve symptomatology. The satisfaction rates were 88% in terms of reduced blood loss. The reduction in volume of uterine fibroids was 37.5% (range 25 to 49%). Histology of fibroids six weeks after laser ablation showed well-defined coagulative necrosis with minimal damage to the surrounding tissue.[60] This may be a useful alternative to open surgery in some patients.

Uterine fibroids are benign tumours of smooth muscle cells of the uterus. They are found in at least 20 to 25% women over 35 years of age. It is estimated that 20 to 505 of these tumours cause symptoms, such as, excessive blood loss, infertility, and recurrent pregnancy loss. They also cause pressure symptoms severe enough to warrant therapy. Fibroids represent the most frequent indication for major surgery in pre-menopausal women. Fibroid growth and maintenance are affected by hormonal cyclical changes. Oestrogen and progesterone receptors have been identified in myomatous tissue and, therefore, fibroids are responsive to therapeutic hormonal manipulation. Since the 1980s, GnRH analogues have been used as a treatment for leiomyomas. These have a temporary effect in bleeding control and reduction of fibroid and uterine size. After therapy is stopped there is, however, regrowth of the fibroids to their original size and recurrence of symptoms. There may be a place for GnRH use in the perimenopausal woman, as she may reach the menopause before surgery is required for the fibroids. Myomectomy is used for patients anxious to preserve or enhance fertility. This operation can often be more difficult than hysterectomy, with increased intra-operative haemorrhage

that can necessitate blood transfusion or hysterectomy. Myomectomy can be performed hysteroscopically, laparoscopically, or by laparotomy. Potential benefits of GnRH preoperatively are decreased blood loss at operation, surgery is technically easier, higher rate of transverse lower abdominal incisions (as opposed to midline incision), and better preoperative haemoglobin. There also appears to be a reduction in operating time for hysterectomy, but not myomectomy.

Administration of GnRH agonist for three months beforehand appears to achieve all the advantages, limiting side effects and cost.[61,62] There are also preoperative ways of reducing blood loss. Some surgeons place a catheter around the uterine vessels during surgery, and this reduces blood loss at the time of surgery. Pitressin, injected into the uterus, reduces the blood loss during surgery. It is a useful adjunct to the use of GnRH analogues preoperatively, in the control of bleeding at the time of surgery.

There are some rare causes of massive gynaecological blood loss. One of these is uterine arterio-venous malformation (A-VM). This can be primary (rare) or secondary, i.e. following curettage or miscarriage. This can cause catastrophic haemorrhage, especially if diagnostic curettage is performed. Case reports in literature[63] describe the successful treatment of uterine A-VM using embolisation, and this would appear to be the treatment of choice in patients wishing to retain fertility. In patients where fertility is not an issue, hysterectomy has been suggested as a permanent cue for this condition.

The general principles of haemostasis in obstetrics and gynaecology are similar to those in other surgical specialties. The properties of uterine muscle and endometrium, especially in relation to pregnancy, however, necessitate the use of some unique methods to ensure haemostasis both in obstetrics and gynaecology.

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Haemostasis in Laparoscopic Surgery and Robotica

Hans-Henning Noelcke, Christina Franke and Karl J. Oldhafer

"*Blood saving is better than blood transfusion!*"

W. Schmitt (1968)[1]

Among intra- and postoperative complications, bleeding represents one of the most serious problems for patients after laparoscopic surgery.[2] Endoscopic surgeons must be trained to recognise, avoid and, if necessary, manage bleeding complications. Over the last decade, novel techniques have been developed to make haemostasis in minimal access surgery as efficient and reliable as in open surgery.[3–8]

Although the technically advanced video-endoscopy provides a better view, including magnification, it can compensate only partially for the lack of direct manual control. Most importantly, major bleeding causes several problems in laparoscopic surgery. In these cases, immediate compression by a laparoscopic instrument or control by

surgeon's hand remains difficult. In addition, suction under laparoscopic conditions makes detection of the bleeding blood vessel troublesome, as gas distension of the abdominal cavity is simultaneously reduced.

Therefore, bleeding complications in minimal access surgery require highly trained teams and several tools for bleeding control. The surgeon should be experienced in endoscopic surgery following the fundamental principle *primum nil nocere* and familiar with the decision to change to open surgery.

To avoid bleeding or to achieve haemostasis in laparoscopic surgery basic instruments and techniques, special equipment, and local haemostyptica are needed.

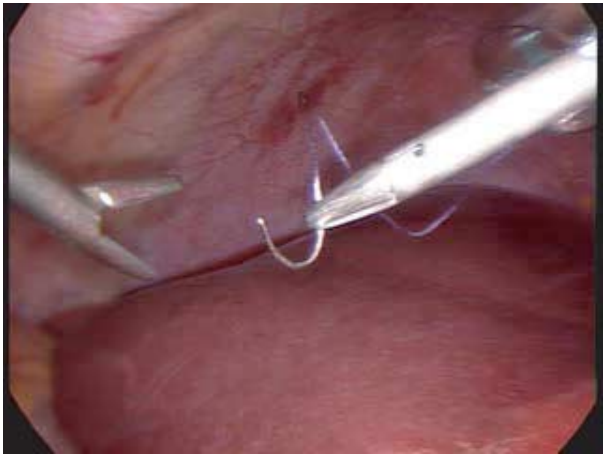
BASIC TECHNIQUES AND INSTRUMENTS

Techniques

Traditional options for achieving haemostasis, such as, suture ligation or purse string sutures are possible, but technically difficult and require well-trained surgeons. These techniques are also time-consuming during laparoscopic surgery (Fig. 1). As in the case of open surgery, different kind of needles and sutures are available. In liver surgery, the Pringle manoeuvre represents a very effective procedure for temporary bleeding control, by occlusion of the hepatoduodenal ligament. The Pringle manoeuvre can also be applied in laparoscopic surgery by placing a tourniquet around the hepatoduodenal ligament. During the occlusion, the bleeding vessel can be controlled by clips or other techniques.

Clips

Basic instruments for haemostasis are clip-applicators for titanium and resorbable clips, which can be used like a ligature to close blood vessels. Clips seal blood vessels by mechanical compression and pose little risk to surrounding tissues when accurately applied. Prior to the application of clips, the vessel must be precisely prepared and clearly identified. Clips may, however, slip or become



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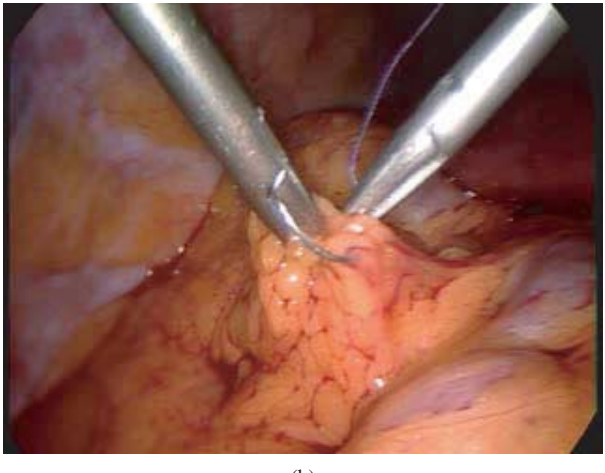


(b)

Fig. 1 Suture ligation during laparoscopic surgery. A 4-0 Prolene with an SH needle is used for bleeding control within the omentum major.

detached and necessitate leaving non-absorbable foreign material within the patient. During surgery, the clips may be dislodged because of tissue manipulation. To overcome this problem, plastic clips have been developed with toothed grasping surface and locking device. In addition, clips can hinder the use of devices, such as, endoscopic

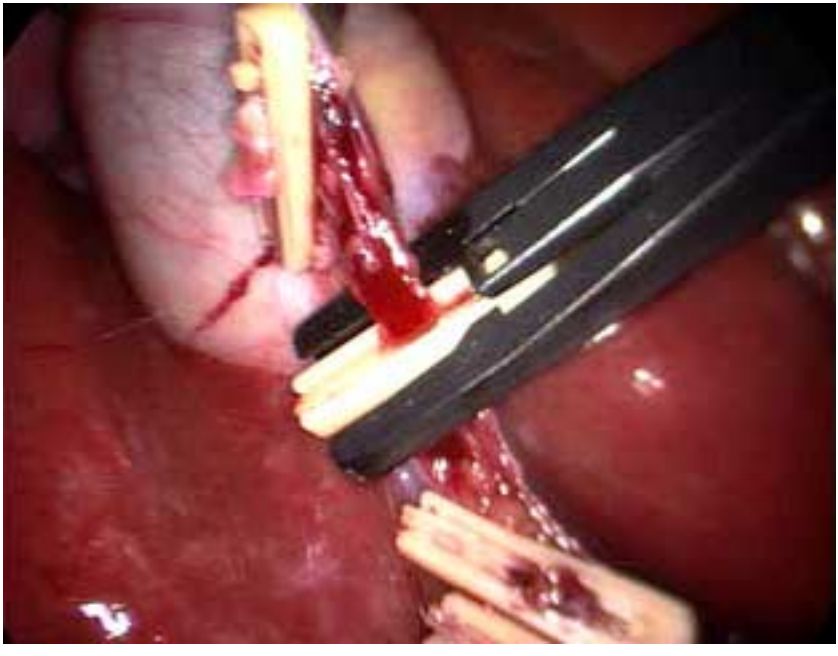


Fig. 2 The picture shows the application of laparoscopic clips for haemostasis during laparoscopic cholecystectomy.

linear staplers because of their bulk.[2] Clip application, however, represents one of the most effective tools to achieve haemostasis (Fig. 2).

Electrosurgery

In high-frequency electrosurgery, electrothermal energy is used for tissue destruction. Frequencies between 500 kHz and 2 NHz do not interference with physiologic electric events, such as, cardiac activity. Different instruments for monopolar and bipolar coagulation, with a diameter between 2 and 10 mm are available. Electrocautery should be applied cautiously and accurately. Excessive use of electrocautery to control haemorrhage is recognised as an important pitfall in laparoscopic surgery. The ease of raising the temperature of tissue many centimetres from the operative site, using monopolar electrocautery, has been shown by several groups.[9,10] Saye *et al.* reported that if a temperature differential of 30°C was reached for only two

seconds, tissue damage occurred.[10] Breaks in the integrity of the insulated coating and the capacitive coupling can occur along the shaft of the instrument or through a metal trocar. When this happens thermal injury to bowel, out of view of the surgeon, may occur as only a small portion of the laparoscopic instrument is visualised during surgery. Up to 50% of laparoscopic bowel injury is caused by electrocautery[11]. Therefore, electrocautery-induced thermal injury leads to significant morbidity and mortality after laparoscopic surgery.[12,13] Another disadvantage of using electrocautery, especially unipolar, is that smoke is produced. This reduces the overview.

SPECIAL EQUIPMENT

The progress in minimal access surgery has led to the rapid development of dissection and coagulation systems and their application tools, to perform complex surgical procedures in laparoscopic surgery and *vice versa*. Energised dissection systems facilitate endocopic dissection and haemostasis and reduce instrument traffic.

Ultrasonic-Dissection

One of the first systems developed in laparoscopic surgery was the ultrasonic-dissector.[14–17] Therefore, the ultrasonically activated scalpel has been modified for use in laparoscopic surgery. It works with shears, usually oscillating at a frequency of 55.500 Hz and leads to a coagulation temperature between 50 and 100°C, while laser and other coagulation devices reach temperatures of 150 to 400°C. Ultrasonic-dissection separates tissue with a cavitational effect and achieves hemostasis by disrupting protein structure and forming a coagulum. It produces minimal local heat. A laparoscopic hook is used for cutting and tamponading tissues and vessels smaller than 2 mm. For larger vessels, up to 3 to 5 mm in diameter, ultrasonic coagulating shears are used. The laparoscopic tools are available as 5 and 10 mm instruments, and they offer the advantage of dividing tissue at the time of coagulation. The local heat to the surrounding region is not as much as in electrocautery, but it does exist.

Electrothermal Bipolar Vessel Sealer

Another type of dissecting and coagulating system is LigaSure®.[18–22] It represents a new generation of instruments that use active feedback to optimise power output and innovative thermal engineering to enable the reduction of excess heat distant from the target region. It works with a combination of pressure and bipolar energy and incorporates impedance based feedback loops to modify the bipolar energy. It leads to sealing of vessels with high resistance against blood pressure and is comparable to a suture or a clip. It is able to close vessels with a diameter up to 7 mm. The blood vessel is fixed by the instrument and compressed with a calibrated force via a ratched scissor mechanism, and a pulse of radio frequency current is applied through the compressed tissue. The initial power level for each application is determined by a fast precusor voltage scan that elucidates the natural impedance of the compressed tissue. Then, by monitoring the temperature-dependent impedance of the compressed tissue during current activation, the microprocessor-controlled feedback loop automatically maintains an appropriate power level until the seal is complete. This process typically takes 1 to 6 seconds. Five and 10 mm instruments are available. A cutting device is integrated into the 10 mm instrument, and this makes the application more comfortable. It has been reported that when LigaSure® was used suture ligature, ties, clips, and other mechanical ligating techniques were rarely required.

Argonplasma-Coagulation

The argonplasma-coagulation has been used for nearly 10 years.[23,24] It follows the principle of unipolar coagulation, however, without direct contact to tissue. The thermic energy is applicated by an ionised argon-flow and is predominantly used for coagulating diffuse bleedings at surface and parenchymatous haemorrhage. The device is available as a 5 mm instrument.

Laser

CO_2-, argon, and Nd:YAG lasers are being used. The effect of laser is primarily thermal.[23] Photonic energy is converted into thermal

energy at the tissue level. The CO_2-laser is the most commonly used laser. It works with a non-contact-technique. The CO_2-laser beam is almost completely absorbed in water. This limits its depth of penetration to a fraction of a millimetre, which leads to a minimal tissue trauma. The Nd:YAG laser is different. It has a much lower absorption in water, leading to thermic coagulation in deeper tissue-layers and enabling haemostatic coagulation of bigger vessels. Argon-lasers act with a combination of coagulation and vapourisation. Up to now, lasers have barely been used in laparoscopic surgery, but clinical trials about laparoscopic cholecystectomy are in progress.[8]

CUSA® and HYDRO-JET®

In order to complete the devices used in laparoscopic surgery to achieve haemostasis, CUSA® and HYDRO-JET® have to be described.[25–27] These devices are primarily used to dissect parenchymatous organs or to perform the total mesorectal excision.[28,29] They help to identify vessels and bile ducts that can be closed by clips or ligature.

CUSA® is an ultrasonic-dissection system that works with mechanical energy. A continuous suction system is integrated, which keeps the tissue close to the oscillating tip of the instrument to increase the efficiency and to clean the operating area. It works with a frequency of 23 or 36 kHz depending on the handpiece. Special laparoscopic tips with a diameter of 2.54 mm are available.

HYDRO-JET® uses a fine, on its surface drilled, laminar jet of water that leads to a highly differentiated mode of application and tissue selection. The pressure is adjustable from 1 to 150 bar. The integrated suction is adjustable from 0 and 800 mm Hg. There are reports on laparoscopic liver resection and nephrectomy as well as on total mesorectal excision.[6,25,28] The application of both systems has been rare in laparoscopic surgery.

Vascular Stapler

Laparoscopic vascular staplers are available with a diameter of 12 mm and different lengths of magazines. They rotate 360° and can be deflect to both sides up to 45°. They are used for closing large vessels

like the splenic artery and the splenic vein within the hilus, during splenectomy or for dissecting the mesocolon, including the inferior mesenteric artery and vein. Compared with other haemostatic devices, vascular staplers are rather expensive.

Harold and co-workers performed an experimental study to compare the bursting pressure of arteries sealed with ultrasonic coagulation shears, electrothermal bipolar vessel sealer, titanium laparoscopic clips, and plastic laparoscopic clips.[21] The authors used arteries from pigs with three different size groups (2 to 3, 4 to 5 and 6 to 7 mm).[21] They found that electrothermal bipolar vessel sealer can be used in vessels up to 7 mm in diameter. In vessels ranging from 4 to 7 mm, it has mean bursting pressures well above physiologic systolic blood pressure. The ultrasonic coagulation shears is effective for vessels in the 2 or 3 mm range. Both titanium and plastic clips achieve substantial bursting pressures for all vessel sizes.[21]

Local Haemostyptica

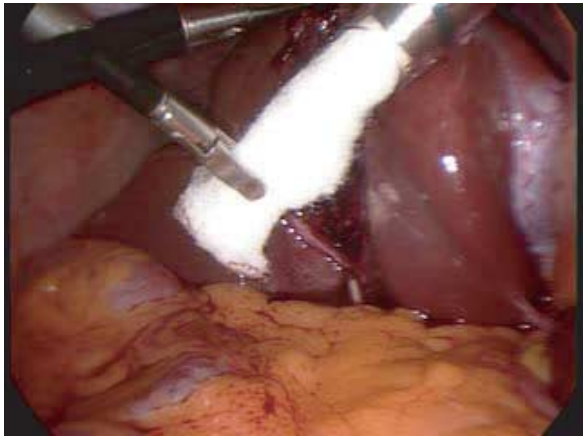
Local haemostyptica are generally applied in open surgery and can also be used in minimal access surgery. Three basic materials are produced in different forms and sizes, apart from fibrin tissue sealant. These are collagen, gelatine, and cellulose.[5,21]

The materials consist of human, animal, or vegetable substances. Indications of application in laparoscopic surgery do not differ from indications in open surgery. Although several application tools are available for use in laparoscopic surgery, most of them can easily be applicated with forceps and reduction sleeves (Fig. 3).

Robotica

The use of robotics is a recent innovation in surgery, and it has led to enhanced dexterity and motion scaling. Remote, accurate telemanipulation of intracavitary instruments by general surgeons, is now possible. Robotic-assisted kidney transplantation is also feasible.[30]

In laparoscopic surgery, two types of assisting technical systems are in use. First, there are devices to hold single instruments that



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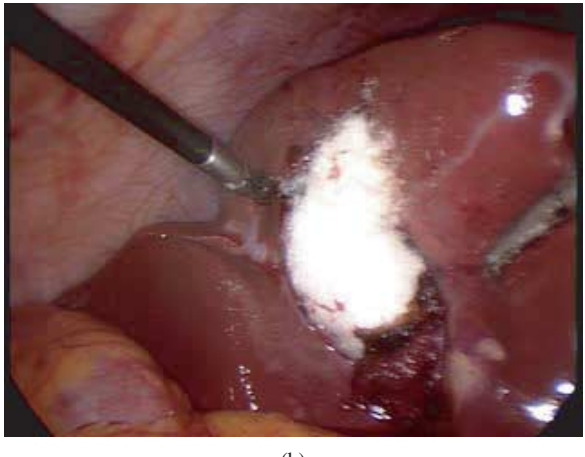

(b)

Fig. 3 The application of local haemostyptica during laparoscopic surgery is depicted.

can be controlled by the surgeon. Second, there are computer-assisted master-slave-systems. Among these, the most frequently used are the ZEUS surgical robotic system and the da VINCI surgical system.[31,32]

Most of them are expensive and, therefore, rather uncommon. The principles and the techniques of haemostasis are the same as in laparoscopic surgery.

CONCLUSION

To perform safe and effective laparoscopic surgery, the surgeon must be well-trained in both basic and advanced surgical procedures as well as in laparoscopic techniques. Furthermore, modern equipment should be available in the surgical unit. Compared with conventional open surgery, all these devices are accompanied with long application times. Unfortunately, there is no instrument that is ideal for all kinds of bleeding problems. The endoscopic surgeon should be familiar with several tools for haemostasis. All of these devices are not necessary, but a particular set of instruments should be available in a surgical department experienced in performing laparoscopic surgery. Most of them are disposable instruments. In times of limited resources it is necessary to decide carefully, which of these tools is the most effective one for the patient and the most potent for the future development of laparoscopic surgery.

Future options in laparoscopic surgery to control major bleeding and loss of gas during suction are possibly, hand-assisted laparoscopic surgery and gasless laparoscopy.[20]

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Haemostasis: A Synopsis of History and Progress — Evaluation of Cross-Linked Gelatin/ Resorcinol/Aldehyde as a Haemostatic Agent and Tissue Adhesive

Rajinder P. Singh, Nadey S. Hakim, Veena Maheshwari and Akshay K. Verma

INTRODUCTION

Scientific exploitation of nature's potential has ushered in an era of tissue adhesives. These are poised to revolutionise surgery, and this review focuses on their significance.

Why is there a search for tissue adhesives and sealants?

A patient with traumatic injury to the abdomen, which results in the rupture of the liver/spleen, is in a state of shock. In this situation,

speedy intervention is the key to survival. On exposure of the traumatised segment of viscera involved, a tissue adhesive can act as a balm to soothe the ailing organ and, therefore, further bleeding can be avoided. Previous time is saved in the process. Sutures have several drawbacks in the sense that many pricks may be required and may cause further bleeding points; they may take time to act as a noose on the right culprit vessels, and they may act as foreign bodies causing reaction. Similarly, diathermy has several drawbacks in the form of inadvertent burning of the structure involved causing a mini funeral pyre and giving the familiar stench of a burning corpse, and the resultant infection and weakness from it. At least, on these fronts, the tissue adhesives have an upper hand as they cause minimal reaction, are less tedious to prepare, can be applied speedily with efficacy, and are systemically absorbed or degraded by body leaving no major damage. Use of tissue adhesives also helps to avoid the constant nudging by a step-motherly body and provides the magical healing touch.

Today, the chief agents for sutureless surgery are the wonder glues that join tissues and seal leaking blood vessels. These include the plastic adhesives called Cyanoacrylate gel or Eastman 910 monomer, the fibrin glue, and the G/R/F glue.

VARIOUS AGENTS USED AS TISSUE ADHESIVES AND HAEMOSTATIC SEALANTS

The various agents used are: thrombin, soluble cellulose, absorbable gauze, haemostasis paper, haemostasis foam, Eastman 910 monomer (methyl-2, cyanoacrylate), absorbable cotton, microcrystalline collagen, gold foil, aluminium foil, alkyl cyanoacrylate, bucrylate (isobutyl cyanoacrylate), enbucrylate (histacryl), G/R/F glue, French glue (GRFG or G/R/A), and haemostasis glue.

A SYNOPSIS OF TISSUE ADHESIVES AND HAEMOSTATIC AGENTS

A difficult problem in surgery has been the control of capillary oozing or of free venous bleeding, especially where the site of haemorrhage

is unsuitable for haemostasis by clip, ligature, or electro-coagulation. Many methods have been suggested to overcome this problem. The most commonly used as well as the oldest method of controlling such bleeding is pressure applied with cotton packs soaked in warm saline or with gauze sponges. Although often successful, this method is time consuming. In 1918, Harvey[1] pointed out and Putnam[2] re-emphasised that a tampon of this drags the clot away from the bleeding point with the recurrence of the bleeding. This fact led to the search for a haemostatic substance, which could be left *in situ* without exciting injurious tissue reaction. Fat, fascia, and muscle were tried initially. The use of muscle, first introduced by Cushing[3] in 1911, remains a satisfactory haemostatic method in difficult situations. Subsequently, two associates of Cushing, Grey[4] and Harvey,[1,5] tried tampons made of both animal and human haemostasis. Histological studies of absorption and resolution of implants of these materials in rabbits, cats, and dogs revealed less reaction than that occasioned by muscle implants. When used either alone or in conjunction with certain fluid clotting agents available at the time, blocks of sterile haemostasis paper were found to be admirable haemostatic agents. In the history of surgery many such fluid clotting agents have been used, ranging from "Koagulen" of Fanio, prevalent in the second decade of this century, to the highly purified thrombins of animal origin that were developed during the past 15 years. In 1943, Putnam[2] reported highly successful results using pledgets of soluble cellulose with animal thrombin and, later, with thrombin of human origin. These became available for widespread clinical use in the course of large-scale plasma fractionation. Fibrin foam, which contained as components only human proteins involved in the natural clotting mechanism, was developed later. This had the properties of an absorbable haemostatic agent, combining the functions of tampon and thrombin. In 1944, Woodhall[6] reported the use of fibrin foam soaked in thrombin in 226 neurosurgical operations and found the required haemostatic effect. This has, however, been available only in limited quantities, and its use is restricted to a small group composed mainly of neurosurgeons. The most recent of the absorbable haemostatic materials is gelatin sponge or foam. An experiment by Jenkins *et al.*[7] in 1945 was devised to determine its behaviour in animal tissues, and it was found to be suitable

as an absorbable haemostatic agent with good properties. It would be a major stride in the history of surgery if an ideal biological adhesive could be produced. It should be easy to sterilise and apply, flexible, non-toxic, absorbable, and non-carcinogenic. In addition, it must remain adhesive in a moist field. Mecrylate was developed in 1960, as industrial glue. In 1966, bucrylate was made available and found to be better tolerated. Later, Enbucrilate (Histoacryl) was synthesised and used in middle ear for adhesiveness. Subsequent histology showed sufficient bone-necrosis warranting care in its usage and the need to limit its dosage to minute quantities. At the same time studies were designed for evaluation of "Fibrin Glue", where, Suzuki *et al.*[8] studied in 1995, its use in the prevention of pancreatic fistulas following distal pancreatectomy. The overall incidence of resulting fistulas was 28.6%.

Cooper and Falb[9] and Koehnlein *et al.*[10] used a new tissue adhesive. It was a gelatin resorcine mixture, which on cross-linking with formaldehyde, formed elastic glue. In 1962, Braunwald and Tatooles[11] used this GRF glue to control hemorrhage from cuts surfaces of liver and kidney of mongrel dogs (published in 1965). Bonchek *et al.*[12,13] later modified the glue and advocated the replacement of formaldehyde by the better bonding formaldeyde-glutaraldehyde mixture. This was used in the repair of dissection of aorta in 1979 by Guilmet *et al.*[14,15] and was called GRFG.

In 1998, it was used by R. P. Singh *et al.* in an experimental study on rat liver at Aligarh Muslim University, India, with good results and no toxicity.

REVIEW OF LITERATURE

Thrombin

The potential use of purified thrombin in the clinic as a haemostatic agent has resulted in the work of isolation and purification of prothrombin and thrombin. The initial preparations were made in 1933 by Mellanby[16] and, later, purified in 1938 by Seegers *et al.*[17,18] and his co-workers. They calibrated and standardised the potency of the thrombin, known as the Iowa unit. Seegers *et al.*[17,18] made the preparation called Thrombin Tropical. According to them, to apply thrombin

to the bleeding surfaces a spray is useful, but a syringe and a fine needle are generally sufficient to flood the surface, with gentle rubbing with the gloved finger. A large group of 102 cases was used for testing, to control bleeding from donor skin graft sites. It was found to be of special use in split-thickness skin grafts. In a total of 78 split thickness-grafting operations of this type, the results were very good. In 40 cases, complete haemostasis was obtained in a few minutes. In 32 cases, there was immediate cessation of oozing. During cholecystectomy, persistent oozing from gall-bladder bed is occasionally very difficult to control. The same author used it in two cases in which sutures were ineffectual, and a prompt check on bleeding was obtained. This preparation was used for mucocutaneous margins, haemorrhoidectomy operations, oozing from mastectomy skin flaps, and cases of delayed postoperative bleeding. There was neither any evidence of local irritation nor hypersensitive reaction, despite repeated use.

Cellulose with Thrombin

In 1942, Uihlein *et al.*[19,20] suggested the use of oxidised cellulose as a haemostatic sealant. Absorbable oxidised cellulose was used as a haemostatic sealant, especially for neurosurgical preparations. Absorbable oxidised cellulose was prepared in the form of transparent gauze-like material and a heavier material that resembled absorbent cotton. The manufacturer also supplied concentrated dried thrombin ampoules. In 1943, Frantz[21] reported the results of some experimental studies with oxidised cellulose, in animals. She stated that it was absorbed when implanted into animal tissues and had little cellular reaction. It was mildly irritating when placed on the surface of the brain. Galbraith[22] also used it in experimental animals after soaking it in a solution of thrombin and applying to bleeding surfaces. Cronkite *et al.*[23] found that a combination of thrombin with soluble cellulose appeared to be of value for local haemostasis in both traumatic and elective surgical procedures.

Uihlein *et al.*[19,20] in 1945 used absorbable oxidised cellulose to try and control oozing and bleeding in 22 surgical, 20 neurosurgical, 11 otolaryngologic, four orthopaedic, and three rectal operations. Excellent, immediate haemostasis was obtained in 37 cases (62%)

and satisfactory in 20 cases (33%), in which, either the gauze-like or cotton-like material was used. In three cases (5%), the cotton-like material failed to control bleeding satisfactorily. Specially prepared absorbable oxidised cellulose, with a solution of thrombin was tried by various surgeons of the Mayo Clinic as an aid to haemostasis, in 60 cases. Haemostasis was excellent and immediate in 37 cases and satisfactory in 20 cases.

Fibrin Foam with Thrombin

A fibrous protein matrix of a wide range of mechanical and biological properties has been prepared from the human plasma proteins involved in the natural coagulation mechanism. This matrix is designed to combine the function of an absorbable tampon with thrombin activity, for use in those instances of haemorrhage where conventional methods fail. Initially, Bering[24] in 1944, worked on the development of fibrin foam. Bailey *et al.*[25,26] in 1944 continued the use of the agents in 1970 neurosurgical patients at the Peter Bent Brigham Hospital and the Children's Hospital, Boston under varying conditions. Its rapid haemostatic action was highly appreciated. The material was left in place in all the patients in amounts varying from small fragments to the size of a golf ball. There was no evidence of cortical irritation in any case. Furthermore, there was no evidence of inflammatory reaction or other unfavorable result in later autopsies. Experiments on monkeys were also carried out, and the earliest tissue reaction in the meninges was the appearance of small numbers of mononuclear and polymorphonuclear leukocytes. This was followed by rapid disappearance of foam with condensation into a more compact mass. The cellular infiltration, never extensive, became minimal and there was a slight proliferation of fibrous tissues. Only very small bits of foam were present after one week, and no fragments at all could be identified at three weeks. One of the most significant contributions to haemostasis has resulted from the large-scale plasma fractionation programme conducted by the department of physical chemistry, Harvard Medical School. One of the products of this was fibrin foam, which Bering[24] described in 1944. Ingraham and Bailey tested this material on the cerebral cortex of monkeys.

Woodhall,[6] in 1944, reported on the use of fibrin foam soaked in thrombin in 226 neurosurgical operations and found that a good haemostatic effect was obtained.

Fibrin sealant has come a long way, and it is being used as a haemostatic agent for operations of heart, liver, and spleen. It is also used for prevention of sarcoma formation after soft tissue dissection, closure of fistulas, and reduced suture vascular and intestinal anastomosis.[27] It was used in nephron sparing surgery by Stojkovic *et al.*[28] in 2005 and was found to be an efficient haemostatic agent for polar resection of kidney. Histology showed less intense and smaller scarring, compared with sutures. Vaiman *et al.*[29] compared fibrin sealant Quixil in a prospective random trial on 179 patients for rates of haemorrhagic complications between bipolar and needle point electrocautery with fibrin glue after tonsillectomy and adenoidectomy. The results of haemostasis were better, with good systemic and local compatibility. Pruthi *et al.*[30] used it for hand assisted laparoscopic partial nephrectomy and found that in addition to haemostatic properties, the fibrin sealant had sealing properties which could prevent urinary leakage. In 2002, Schenk-Worthington *et al.*[31] conducted a prospective, random study to test the efficacy of fibrin sealant in PTFE graft replacement for dialysis in upper limb and found it to be a superior haemostatic agent in this vascular procedure, compared with gelfoam, thrombin, and surgical. In an experimental study on rabbits, Kheirabadi *et al.*[32] compared the efficacy of common haemostatic agents in the fibrin sealants and assessed the functional strength to secure haemostasis in lieu of placing extra sutures. They found fibrin sealant to be most efficacious, with the potential to ease the anastomosis and shorten the duration of the vascular procedure. Nervi *et al.*[33] used fibrin sealant in burn patients in 2001, to test its efficacy as topical haemostatic agent in a multi-centre clinical trial. Fibrin sealant was efficacious, significantly decreased time to haemostasis at the donor skin harvest sites, and had no adverse reactions. In 2000, Paulson *et al.*[34] found it to be effective in reducing post-procedural bleeding after open liver biopsy in anticoagulated and non-anticoagulated swine. Fibrin glue was also used successfully for skin graft fixation by Buckley *et al.*[35] in 1999. All patients had more than 90% take with no adverse reactions or infections. In another multi-centre, prospective,

random trial Atkinson *et al.*[36] tested the efficacy of fibrin sealant as haemostatic agent at the cannulation site in neonates undergoing ECMO (extracorporeal membrane oxygenation). The fibrin sealant was solvent/detergent treated and plasminogen depleted. The results were good.

Concerns of viral transmission with blood and blood products exist. Hino *et al.*[37,38] reported iatrogenic human parvovirus B19 infection resulting from the use of the same batch of fibrin sealant under operation.

Fibrin Glue and Oxidised Cellulose Sandwich

This was used by Finley *et al.*[39] from 2002 to 2003, in patients undergoing laparoscopic non-hilar wedge resection of small renal lesions, without vessel clamping. They achieved excellent haemostasis.

Fibrin with Collagen

Ueda *et al.*[40] studied TO-193 (TachoComb), a new fibrin adhesive consisting of collagen sheet coated with fibrin glue, on several experimental models. They found it to have a strong and potent adhesive effect as well as haemostatic effect. It also significantly reduced bleeding in liver resection of normal rat.

Gelatin Sponge with Thrombin

A recent addition to the absorbable haemostatic agents is the gelatin sponge or foam. This is prepared from ordinary commercial gelatin, which is made up in a solution to which a hardening agent is added. After bubbles of air are removed, the mixture is allowed to dry in cans. It can then be cut into any required size or shape. The material has been used for experimental purposes and has been provided in sealed glass jars previously subjected to sterilisation with dry heat. The sponge will take up many times its weight of water when it is submerged and the air bubbles expressed. It does not fragment easily, although it is not especially tough. Gelatin is a protein, which is non-antigenic, a factor to be acknowledged. Jenkins *et al.*[7] in 1945,

carried out an experiment on a series of 12 dogs to test the behaviour of gelatin in their tissues. Incisions were made 2 cm long and 1cm deep in the liver, the kidneys, and the spleen. The brisk haemorrhage resulting from the incisions was controlled by packing the moistened gelatin sponge into the incision and holding it in place for about two minutes with ordinary, moistened gauze. When the gauze was removed, the gelatin sponge was usually found adherent to the incision and the bleeding stopped. Sometimes, there was oozing from the ends of the incision, which was averted by placing another piece of gelatin sponge over the length of the incision. Gelatin sponge was also implanted in the omentum and in the rectus muscle near the abdominal incision. The animals were sacrificed at periods varying from two to 56 days after the implantation. Two of the animals died at two and three days, respectively. At autopsy the sponge was usually identified easily in the short-term implants as a red soggy mass. In the omentum there was an area of induration, in the centre of which the sponge could be found if the omentum was cut across at the point. After a week or ten days it was often difficult to identify the sponge in the abdominal wall, and in the omentum one could find only a slightly indurated area in which the sponge could be found. After two weeks it was difficult to identify the sponge grossly in the omentum. The sponge was usually identified easily in the early specimen of liver, kidneys, and spleen. Varying amounts of fibrinous adhesions were present about the implants in the liver, although they were not common in the kidney or the spleen. Microscopic sections were made of all the implants that could be identified either grossly or as a residual fibrous adhesion. The gelatine sponge appeared as a meshwork of homogenous haematoxylin-staining material. Where the sponge had been used for haemostasis, as in the liver, the kidney, and the spleen the interstices of the sponge were seen filled up with red blood cells. In some sections, there was evidence of invasion of the peripheral portion of the sponge by polymorphonuclear leukocytes and, in these cases too, there was evidence of absorption of the gelatin sponge. There were also some lymphocytes and plasma cells in the periphery. After a week, the predominant cells invading the gelatin sponge were macrophages. There was little tendency for the formation of foreign body giant cells. Fibroblast response was usually

observed within a week, producing a definite encapsulation of the sponge. Subsequently, this encapsulation became fibrous. Sinclair and Douglas[41] in 1944 found that the local implantation of gelatin into wounds led to accelerated fibroplasia and increased strength. The gelatin sponge was used in 15 clinical cases in various ways to determine its behaviour in human tissues. It has been used in the incisions in the liver to obtain specimens for liver biopsy, on the undersurface of the liver after cholecystectomy, on thyroid beds after thyroidectomy, on dermatome donor areas, in laparotomy wounds, and on the surface of granulating wounds. According to the authors, however, the observations were too limited to draw conclusions other than that bleeding was controlled and there were no complications that might be attributed to the gelatin sponge. Jampolis *et al.*[42] and Jenkins *et al.*[43] in 1947, conducted a series of 15 experiments on dogs and found it possible to control haemorrhage from relatively large wounds of the right or left vertical with a "Patch" of gelatin sponge, without any supplementary suture or the use of thrombin in the sponge.

Gelatin matrix thrombin tissue was used as an effective haemostatic agent by Bak *et al.*[44] during laparoscopic partial nephrectomy in the period 2002 to 2003. The two-component sealant comprised of a thrombin component and gelatin matrix granula. It was applied after tumour resection and before reperfusion of kidney. Haemostasis was immediate after application of the agent for one to two minutes, to the moist resection zone. There were no cases of postoperative bleeding.

Plastic Adhesives (Cyanoacrylates)

During the past ten years, new adhesives have been developed whose properties surpass those of any of the older, better known organic adhesive compounds. One of these is the cyano-acrylate monomer, known more commonly as the Eastman 910 Adhesive. It is a colourless liquid which, in the monomer form, has the appearance and the viscosity of water. When it is applied to any surface in a thin film a polymerisation reaction occurs, and it becomes a tough solid. Polymerisation takes place within a few seconds. The time varies between two and 30 seconds, depending on the material and the amount of

moisture present. The reaction takes place remarkably rapidly, and the bond is firm and permanent. When a violent effort is made to break the bond, most substances will separate in a plane other than that which was recently joined. One of these adhesives was methyl-2 cyanoacrylate (Eastman 910 monomer), developed in 1960 as industrial glue. In 1960, bucrylate was made available, and it was found to be better tolerated. Heumann and Steinbach[45] undertook a study, in which, 50 healthy rabbits were used. In one group, the incudostapedial joint was dislocated with a small hook. The ossicles were subsequently re-united with enbucrilate (Histoacryl). The histological examination of the evaluated ears showed a severe tissue reaction to the enbucrilate. Advanced erosion of the bone at the site of application of the glue on the ossicles was found. The adhesive was present in the middle ear of some of the rabbits, three months after surgery. The enbucrilate was also found to be embedded in granulation tissue surrounded by foreign body giant cells. In 1963, Mathes and Terry[46] conducted a study on six mongrel dogs (12 kidneys) to evaluate Eastman 910 monomer adhesive's efficacy for non-suture closure of nephrostomy. Eastman 910 adheres to moist living tissues and is sterile, but it is not flexible when dry and is somewhat initiating to the tissues. In 75 cases of nephrolithotomy, 24 complications occurred and 11 patients required nephrectomy. The rate of secondary haemorrhage was 9%, as reported by Jordan and Tomskey.[47] Other investigators have studied the use of No. 910 adhesive for re-enforcement of maxillo-facial injuries and cerebral aneurysms, corneal grafts, non-suture closure of arteriotomy incisions, closure of the pericardium about a flanged cannula during cardiac surgery, and non-suture closure of vena cava linear and circumferential incisions.

In Japan, Inou[48] used this adhesive to successfully close more than 70 laparotomy incisions, without conventional sutures. Recently, Clark[49] used this adhesive to seal the severed ends of the anterior jugular vein without sutures, in a man who underwent radical neck dissection. He reported no complications after a month. He also reported 168 successful vein repairs in 170 dogs with the adhesives alone. There were two instances of bleeding. In 40 dogs, whose venae cavae were repaired with the adhesive alone by Healey *et al.*[50] in 1961 and associates, there were no deaths due to haemorrhage, thrombosis

or infection at the site of repair. After three months the site of incision could be detected only with difficulty.

In 1962, O'Neil *et al.*[51] conducted a study for non-suture intestinal anastomosis that did not employ the principle of applying serosa to serosa and did not result in inversion of the bowel wall. Twenty-six mongrel dogs were used for this purpose. There were five failures, four of which occurred in the large intestinal group and one in the small intestinal group. The failures in the large intestinal group presented a common finding of necrosis of the entire intestinal wall on either side of the anastomosis and complete disruption of the anastomosis leading to generalised peritonitis and death. The failure of the small intestinal group also showed histological evidence of extensive necrosis, but grossly the anastomosis was intact. In 1962, Fischl[52] used the Eastman 910 monomer adhesive for primary closure of skin incisions. The first attempts were made on segments of excised skin. These were successful, and the skin margins adhered well. Since then, it was used to close incisions on the skin of laboratory animals. Five mongrel dogs were used and 15 incisions made on them. Thirteen of them healed without incident. The vigorous scratching by one dog disrupted the other two. No toxic effects were encountered.

Fibrin Glue

Fibrin glue is made with highly concentrated human fibrinogen and clotting factors achieving haemostasis. The fibrin adhesive consists of dried sealer protein concentrate, aprotinin, dried thrombin, and calcium chloride. Sealer protein concentrate is made from donor human plasma. Kram *et al.*[53] used fibrin glue (FG) in 1987 for achieving haemostasis in superficial and deep hepatic injuries. The experimental study was done on 12 adult, mongrel dogs. Half of the dogs received two penetrating hepatic injuries each, and the other half underwent resection of a large segment of left lobe of liver. Haemostasis was achieved by applying FG into and over the bleeding wounds without hepatic arterial occlusion. Complete haemostasis was achieved in all animals before skin closure. One dog from each group was re-exposed and the liver specimens harvested for gross and microscopic examination at postoperative intervals of 12 hours,

24 hours, and two, three, six, and eight weeks. There were no cases of intra-abdominal infection, abscess formation, or bile fistulae. Histological examination showed a thickened capsule containing fibrous connective tissue and neovascular proliferation. There were no signs of local or systemic toxicity. One dog died on the postoperative day 1 due to re-bleeding from the hepatic injury, but all others survived without complications.

Subsequent studies were conducted by Kram *et al.*[54] in 1985 to repair trachea with fibrin glue. Eight mongrel dogs were taken for the experiment, and a large partial transaction was made through the anterior tracheal wall between the sixth and the seventh tracheal rings. One absorbable suture was placed around the tracheal cartilages. FG was applied over the incision and allowed to harden. At five-minute intervals, two additional layers of FG were applied. All dogs survived with intact anastomoses, with no postoperative air leaks or complications. Later Kram *et al.*[55] studied the use of fibrin glue for sealing pancreatic injuries, resections, and anastomoses. Postoperatively, no patient developed pancreatic fistulas, pancreatic abscesses, or pseudocysts. In 1995, Suzuki *et al.*[8] studied the role of FG in the prevention of pancreatic fistulas following distal pancreatectomy. The overall incidence of pancreatic fistulas was 28.6%, but that in the fibrin glue group was 15.4%. Kuderna *et al.*[56] evaluated the repair of several peripheral nerves using FG. Nerve repair requires the junctions to be free of tension, and sutures were used for stabilising the junctions, which lead to foreign body reaction. Instead of a suture, FG seal was used for stabilising the junctions, and the results were encouraging.

Metallic Films

In 1964, Gallagher and Geschickter[57] reported several experimental and clinical *in vivo* applications of commercial gold leaf. They used it for haemostasis and prevention of adhesion between dura and brain. Later, in the same year, Kanof[58] used the gold leaf successfully in treating cutaneous ulcers of the lower extremities. Porter *et al.*[59] evaluated the use of gold leaf on mongrel dogs, by covering experimentally induced hepatic defects with the foil. Films with thickness of

0.0000036 and 0.0000072 inches were successfully used in transected hepatic surfaces in every case, and haemostasis was achieved. In 1968, Dardik *et al.*[60] used the foil on renal hilar vessels of rats, with good results.

The G/R/F Glue (Gelatin-Resorcinol-Formaldehyde Glue)

A new tissue adhesive which was an elastic glue formed by cross-linking gelatin resorcine mixture with formaldehyde, was tested by Cooper and Falb[9] and Koehnlein *et al.*[10] It was found to have a better bond strength than other systems tested, viz. isocyanates, Eastman 910 monomer, and gelatin formaldehyde. In 1966, Braunwald and Tatooles[11] conducted an experimental study on mongrel dogs and evaluated the usefulness of this modified G/R/F in controlling bleeding from standardised surgical injuries on their liver and kidneys. A solution was made with gelatin and resorcinol in 3:1 ratio and total solid content of 60 to 70%. The mongrel dogs were divided into two sets. In the first set of 25 dogs, a 3 by 2 cm portion of liver was excised in 12 animals, and a portion of the lower pole of the kidney was amputated in 13 animals. After ligating the large arteries on the cut surface of organs, a few drops of 37% formaldehyde U.S.P. were applied to the tissue surface, followed by the application of semi-liquid G-R mixture, which had been converted from the gel state to the sol state by warming to 40°C. One or two additional drops of formaldehyde were, then, added to the mixture. In the second set of animals, after a similar surgical procedure, a mixture of acidified G/R solution and formalin (5 ml of semi-liquid G/R acidified to a pH of 4 with 0.1 HCl and three drops of 37% formaldehyde) was applied onto the injured surface of liver and kidney, instead of a direct application of concentrated formalin on the tissue surface. This was followed by a fine spray of sodium bicarbonate powder, blown over the tacky adhesive from an atomizer bottle to raise the pH *in situ* and trigger the cross-linking reaction. All the animals were sacrificed at one- to six-month intervals and autopsied, excepting the two dogs of the first group that died of wound infection in the immediate postoperative period. On autopsy, a few filmy adhesions were seen about the operative site and surface of the liver and the kidney had healed well. Some residual gelatin was

still visible on the surface for a few months and by six months only scar was visible. Microscopic examination revealed the presence of a small amount of residual glue up to six months and the removal of fragments of gelatin by macrophages and subsequent fibrosis. Initial polymorphonuclear leukocytes were replaced by a chronic inflammatory response with passage of time. While the tensile strength of the bond was comparable in both groups of animals, haemostasis was quick in the second group (two to three minutes). In the first group, several millimetres deep area of focal necrosis was often present at the site of application of formaldehyde, which was not the case in the second group. In addition, in the second group the total amount of formaldehyde used was considerably less, and the risk of accidental spillage of formalin on the tissues was averted.

Bonchek *et al.*[12,13] later modified the glue by replacing formaldehyde by the better bonding formaldeyde-glutaraldehyde mixture. This was used in the repair of dissection of aorta in 1979 by Guilmet *et al.*[14] and was called GRFG or G/R/A.

GRF has been extensively used as a haemostatic adjunct for vascular and cardiac operations.

Dapper *et al.*[61] have used argon beam coagulator for bonding cross-linked gelatin fibres to heart muscles, lung pleura, and parenchyma. Rittoo *et al.*[62] used GRF glue as a sealant of PTFE patch suture line with good results and no compromise of the characterisation of the patch.

Ünlü *et al.*[63] compared the use of fibrin glue, GRF, and collagen on a rabbit vascular graft model, for preventing suture hole bleeding. All were found to reduce blood loss, but fibrin-containing factor XIII was the most effective. Hata *et al.*[64] have used GRF to aid operations for type-A aortic dissection with reasonable early and late mortality rates. There was no histological evidence of adverse tissue reaction. Nakajima *et al.*[65] concluded in their study that the cause of re-dissection after surgery for type-A aortic dissection using GRF glue, is not too much formalin.

Suehiro *et al.*[66] found a high incidence of redissections of aortic root and false aneurysms and aortic insufficiency subsequent to surgery for acute aortic dissection using GRF glue. Tsukui *et al.*[67] found coronary ostial stenosis between interposition graft and

coronary artery attributable to inappropriate use of GRF glue. Kazui *et al.*[68] concluded that GRF was associated with a certain risk of aortic wall necrosis when used for re-approximation of layers of dissected aortic root and suggested proper use of these glues. Bingley *et al.*[69] undertook a study in their institution over a 5.5-year period with the intention of picking up complications of GRF glue used in cardiothoracic cases, especially acute type-A dissections and paediatric cardiac cases. They found unsatisfactory, long-term complications related to the glue, and they discontinued its use in these groups.

Gelatin/Resorcinol/Formaldehyde/Glutaraldehyde Adhesive

Use of formaldehyde gives a superior initial bonding, while glutaraldehyde appears to have greater durability *in vivo*.[12,13] A combination was, therefore, considered for optimal adhesive properties. The G/R/F glue, after disappearing from the surgical scene for some time, was re-introduced by a French group as GRFG (also then called the French glue) in 1979. The French group, Guilmet *et al.*[15] described its use in aortic dissection. In 1982, a clinical series in aortic surgery involving the use of GRFG as an adjunct to prosthetic graft implantation was published by Bachet *et al.*[70] Another series described the technique of complete re-fixation of the dissected layers in the ascending aorta and the aortic arch without any prosthetic material.[71,72] Bellotto *et al.*[73] studied pneumostasis of injured lung in rabbits with Gelatin-Resorcinol-Formaldehyde-Glutaraldehyde tissue adhesive. They evaluated the ability of the adhesive to seal incisional air leaks promptly in the lungs of rabbits during persistent ventilation and positive intratracheal pressure. They also assessed the shelf life of the non-proprietary formula by testing its efficacy at intervals and established a technique for application of the adhesive. They found it to be an effective pneumostatic giving a consistent decrease in the magnitude of air leak and complete pneumostasis in most of the cases, in the presence of clinically relevant positive pressure ventilation. In 2000, Nomori *et al.*[74] used GRFG glue for sealing pulmonary air leakage during lung surgery. They mixed formaldehyde-glutaraldehyde jelly with 2.5% carboxymethylcellulose to increase its viscosity. They found the glue to be safe and effective in preventing pulmonary air

leakage from deeply cut lung. In 1999, Hata *et al.*[75] concluded that the glue was good enough for improving long-term survival and to reinforce the diseased aortic wall after surgery for type-A aortic dissection, but it was not found to have sufficient haemostatic effect for use in anastomosed stitches from the outer side of the aortic wall.

In 1998, the authors, R. P. Singh *et al.*, tested the efficacy of this promising glue as a haemostatic agent, sealant, and tissue adhesive in the liver of rat in an experimental setting in the Animal House of J. N. Medical College, Aligarh Muslim University, India. Gelatin/Resorcinol/Aldehyde (GRA) glue was prepared in two separate forms, i.e. the adhesive and the activator. The adhesive was prepared by mixing gelatin and resorcinol in 5:1 ratio weight/volume (w/v) and diluting the mixture with distilled water to a concentration of 60% w/v. A mixture of formaldehyde (9.25%) and glutaraldehyde (25%) in 9:1 ratio (volume/volume) was used as the activator to initiate cross-linking. The adhesive was packed in plastic syringes and the activator in medicine droppers. Both were to be mixed in equal volumes, just prior to application. Twenty-eight albino rats, weighing 125 to 150 grammes were used for this study. They were divided into four groups: A, B, C, and D, each comprising of seven rats. The rats were anaesthetised with ketamine. The abdomen was opened by a 5 cm long right subcostal incision, and the liver was exposed. While supporting it with a finger behind it, a wedge defect, about 1cm long and 0.5 cm deep was created in its most accessible part, usually the median lobe or the left lateral lobe. Profuse bleeding often ensued and was controlled by:

1. Applying freshly constituted and activated GRA glue on the cut surfaces.
2. Applying proximal manual pressure on the liver to control oozing, if it was persistent.
3. If this failed, haemostasis was achieved by re-application of the glue.

The haemostasis achieved was graded as excellent (1), satisfactory (2), and poor (3).

The wedge of liver was, then, apposed with the defect in the liver having glue on its surface and held in place for some time. The

pressure was released every 15 seconds, and the time taken for the adhesion of the two cut surfaces was noted. The liver was released and the abdomen closed in layers. Harvesting of the rats was undertaken on specific days for each group (group A-7 days, group B-14 days, group C-21 days, and group D-28 days). During autopsy, the site of repair was evaluated for its visibility, disruption, haematoma formation, adhesions, necrosis signs, and residual glue amount. Samples of the repaired segment of the liver were obtained for histopathological examination. During operations, haemostasis was excellent in most cases, except one where two applications of the glue were needed. Haemostasis was graded as excellent in 71.4%, satisfactory in 25.0%, and poor in 3.6% cases. Mean (± SD) time for tissue adhesion was 2.6 minutes (Range: 2.4 to 2.7 minutes). All except one rat maintained good general condition in the postoperative period. This rat, belonging to group A died six hours after operation, presumably due to anaesthetic complications. Five rats developed wound infection that was managed with systemic antibiotics and local povidone iodine. The site of repair was visible in 50.0% of cases on day 7, 28.5% each on days 14 and 21, and 14.3% on day 28. Visible adhesions decreased from 66.6% on day 7 to 28.5% on day 28. Residual glue was seen in 33.3% cases on day 7 and, in none, on day 28. In the rat that died at six hours, small haematoma and fissure at the site of repair were noted. No other rats showed signs of disruption of wound or haemorrhage at the wound site. No necrosis was seen in any case. There was no bile leakage in any of the cases studied, showing good sealant property of the glue. Residual glue was present even up to 28 days, although its amount gradually decreased from 83.3% on day 7 to 43.0% on day 28. Subcapsular haemorrhage was seen only in the cases seen early. The rat that died on day 0 had subcapsular haemorrhage; this was also seen in 83.3% cases on day 7, but in none of the cases on subsequent days. An acute inflammatory response with predominantly neutrophils, eosinophils, and RBCs was noted on days 0 to 7. Mononuclear cells from day 14 gradually replaced the cellular response onwards. There was no evidence of fibrosis in any of the cases on day 7. It was present in 28.6% cases on day 14 and in 85.7% cases on day 28. Necrosis was not seen in any of the cases, and there were no foreign body giant cells. On statistical analysis, a significant decrease in subcapsular

haemorrhage was observed. The authors experienced initial difficulties commensurate with the learning curve in the study. Therefore, two applications of glue were required in some of the initial experiments. In all remaining cases, however, haemostasis achieved was excellent. The decreasing trend in visibility of site of repair and residual glue was seen with passage of time. Despite the fact that no residual glue was seen upon naked eye examination, it could be identified microscopically in 43% of cases on day 28. Evidently, longer follow-up is needed to determine the time frame within which the glue is completely absorbed. Other authors have reported microscopic evidence of glue up to six to 16 weeks in experiments involving organs in different animals. Koehnlein *et al.*,[10] however, reported the absence of glue in four to six weeks. Ennker *et al.*[76] using GR-DIAL glue in rabbit lungs found good adaptation of surfaces and progressive disintegration of glue with time, with good bio-resorption, when the incision was closed with a thin layer of glue. These differences may be explicable on differences in experimental methods, animals, and organs involved. In this experiment, adhesions were found to decrease with time. This was in keeping with the gradual absorption of the glue. A disproportionate amount of adhesions could be attributed to experimentalists' initial unfamiliarity with the procedure. Some adhesions in group A were also noted to be distant from the defect, perhaps due to spillage of glue. Barring these few initial cases, adhesions were limited to the site of repair. Furthermore, most of the adhesions were flimsy and could easily be separated with finger, causing no bleeding on separation. Several other authors have similarly reported no adhesions or a few flimsy adhesions at various sites in different experimental settings.[12] A few, however, noted extensive sub-pericardial adhesions that were difficult to separate with finger.[77] The divergent results are likely due to differences in experimental subjects and methods. GRA was found to provide excellent haemostasis and tissue adhesion. It had good sealant property. Mean time for tissue adhesion was 2.6 minutes. The bond formed was pliable flexible and not hard in consistency, as was in the case of plastic adhesives. No prior sterilisation of the GRA mixture was needed, perhaps on account of the bacteriostatic properties of resorcinol and the aldehydes. It did not produce any tissue necrosis in the liver. The glue is cheap and easily prepared and stored. It also

has a good shelf life. Prior to its use in humans, however, further studies and long-term follow-up are needed to evaluate its carcinogenicity and teratogenicity.

Modified Gelatin and Polysaccharides

Mo *et al.*[78] modified gelatin with ethylenediamine, using carbodiimide. Dextran and hydroxyethyl starch were oxidised by sodium periodate. By mixing the two a Schiff base was formed, which resulted in cross-linking and gel formation. Fastest gel formation was in two seconds, and bonding strength to porcine skin was 225 gf cm^{-2}.

Formaldehyde-Free Glue

Fibrin glue has good biocompatibility, but its adhesive strength is relatively low. The modified GRF glue developed in the 1960s appeared to be a viable solution. Further modifications were made in the 1980s because of the continued controversy concerning the possible carcinogenicity and mutagenicity of formaldehyde. These modifications were aimed at replacing the formaldehyde component with aliphatic dialdehydes. Ennker *et al.*[79] studied the use of formaldehyde-free collagen glue in experimental lung gluing. They replaced the formaldehyde component of GRF glue with two less toxic aldehydes, pentanedial and ethanedial. In this manner, two-component glue was produced. The first component, a gelatin-resorcinol condensate, has the viscosity of honey, while the second component, a mixture of dialdehydes, is a watery solution. To evaluate the adhesive strength of this new glue, GR-DIAL, lung incisions in rabbit hybrids were glued together. Each group ($n = 5$) was examined histologically after two days and one, two, and four weeks. The glue disintegrated gradually with good bioresorption when the incision was closed with a thin layer of glue. The healing process was favourable, indicating good biocompatibility. Therefore, GR-DIAL glue was capable of enhancing the use of surgical glues in the field of thoracic surgery by enabling surgeons to close larger parenchymal lesions than with fibrin glue.

Among the dialdehydes, pentane-1.5-dial and ethanedial (IUPAC nomenclature for glutardialdehyde and glyoxal) proved to be

the most effective in earlier experiments. *In vitro* trials on lung parenchyma indicated that fibrin glue, which of all the clinically applied glues was currently the most widely used, had the least adhesive strength. In addition to fibrin glue and GRF glue, cyanoacrylate glue and various pentane-1.5-dial/ethaneidal ratios of GR-DIAL were also tested in different experimental settings. These *in vitro* evaluations indicated that cyanoacrylate glue had the strongest adhesive power, but had the disadvantage of becoming a stiff layer of artificial material with no elastic properties, forming a nearly impenetrable barrier in the region of the elastic lung tissue. Its biocompatibility was poor, and its adhesive power decreased in humid conditions. Therefore, cyanoacrylate glue was ruled out as the optimal adhesive for use in lung parenchyma. After cyanoacrylate glue, GRF glue showed the second-best adhesive power in dry conditions. On humid surfaces, however, GRF glue was surpassed by the adhesive strength of GR-DIAL glue. If pentane-1.5-dial alone was used as the hardening component, the adhesive power of GR-DIAL reduced slightly. In addition, as ethanedial is less toxic than pentane-1.5-dial, it was not desirable to use only pentane-1.5-dial for the second component. Although these two aldehydes are less toxic than formaldehyde, it was concluded that it would be necessary to perform extensive toxicity studies, including resorption kinetics before clinical use can be sought.

Newer Variants of Gelatin Resorcinol Glue

Considering the potential toxicity of formaldehyde or glutaraldehyde, Sung *et al.*[80] from Taiwan suggested that the cross-linking method of GRF be changed. They used an epoxy compound (GRE glue), a water-soluble carbodimide (GAC glue), or a genipin (GG glue) to cross-link with gelatin as a new adhesive. In their comparative study, they concluded that GRE glue is not suitable for bioadhesion in clinical applications. GRF and GRFG glue may be used when their ability to bind tissue tightly and rapidly is needed. They also concluded that GAC and GG glues can be used when minimal cytotoxicity and stiffness are required during adhesive action. In 1995, Basu *et al.*,[77] in their comparative study between cryoprecipitate glue, French glue, and two-component fibrin sealant in controlling

suture line and surface bleeding from standardised atriotomy and aortotomy, concluded that GRFG glue is a good tissue reinforcer; fibrin sealant is preferable as a haemostatic agent if accompanied with a mechanical barrier; and cryoprecipitate glue maybe used when haemostasis is the only concern.

In 2000, Chan *et al.*[81] conducted an experiment on swine model of splenic haemorrhage to compare Poly-N-Acetyl Glucosamine (P-GlcNAc) with absorbable collagen (Actifoam), fibrin sealant (Bolheal), and surgicel. P-GlcNAc was found to be more effective and promising as a topical haemostatic agent in both unheparinised as well as anticoagulated animals.

CONCLUSION

The world of surgical glues has definitely expanded, and the haemostatic agents have established their place in several clinical settings after passing through a test of fire.

All the glues have their advantages and disadvantages. Concerns about viral transmission with fibrin glues, hard consistency of plastic adhesives, and potential toxicity with GRF glue are the limiting factors.

Although they have come a long way from the time they were first discovered, a lot of ground remains to be covered. Good quality research is definitely paving the path towards the ideal solution.

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INDEX