Perioperative Coagulopathies and Management

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INTRODUCTION

The coagulation system involves a cascade of factors responsible for maintenance of haemostasis in the body. This system is not only made for forming clots but is also involved in tissue repair, defence against micro-organisms, autoimmune processes, arteriosclerosis, tumour growth and metastasis. Surgical procedures often cause imbalance of this system, leading to a tendency to either thrombosis or bleeding. Operative intervention, clinical risk factors including immobility, infections, anticancer drugs and various other perioperative factors such as hypothermia, metabolic acidosis, volume expanders and extracorporeal circulation are increasingly being demonstrated to interfere with the coagulation system.

The coagulation system

The main cellular components of the coagulation systems are platelets, endothelial cells, monocytes and erythrocytes. The main molecular components are the coagulation factors and inhibitors, fibrinolysis factors and inhibitors, adhesive proteins like von Willebrand factor (vWF), intercellular proteins, acute-phase proteins, immunoglobulins, calcium ions, phospholipids, prostaglandins and certain cytokines. Despite this significant diversification, the coagulation proteins are the core components of the haemostatic system, forming a complex interplay that involves the following steps. [1]

(a) **Initiation:** Tissue factor (TF) expressed by the damaged vascular bed binds FVIIa (which circulates in small quantities) triggers coagulation by activating FIX to FIXa and FX to FXa. FXa then binds very rapidly to FII, producing small amounts of thrombin (FIIa). In a much slower reaction, FIXa binds to and activates FX to FXa. Most coagulation processes in vivo are considered to be initiated by tissue factor, whereas the clinical significant contact activation (activation of FXII) is probably caused by RNA from disrupted cells and may be the long-sought FXII activator.

(b) **Amplification:** The amount of thrombin generated at this stage is too small to activate fibrinogen to fibrin. But, there are several feedback amplification mechanisms. First, generation of FVIIa is increased by activation of FVII bound to tissue factor by FVIIa, FIXa and FXa. Thrombin then activates the non-enzymatic cofactors FV and FVIII, which accelerate the activation of FII by FXa and of FXa by FIXa, respectively. In a further feedback loop, thrombin also activates FXI to FXIa, increasing the generation of FIXa.

(c) **Propagation:** To maintain continuous thrombin generation, ensuring the formation of a sufficiently large clot, large amounts of FXa are produced by the activation of FX by FIXa and FVIIIa (intrinsic tenase complex). FIXa stems primarily from the activation of FIX by the FVIIa-TF complex.

(d) **Stabilization:** Maximum thrombin generation occurs after the formation of fibrin monomers. Only then is the amount of thrombin high enough to activate FXIII, a transglutaminase, which then cross-links the soluble fibrin monomers to a stable fibrin meshwork. Thrombin then activates the thrombin-activatable-fibrinolysis-inhibitor (TAFI) that protects the clot from fibrinolytic attack. For the first several hours after surgery there are marked increases in tissue factor, tissue plasminogen activator, plasminogen activator inhibitor-1(PAI-1) and vWF, leading to a hypercoagulable and hypofibrinolytic state, as evidenced by increased generation of coagulation activation markers, such as thrombin–antithrombin complexes, fibrinopeptide A and many others. The levels of these mediators are known to fluctuate rapidly and their degree of perturbation is dependent not only on the type, degree and duration of surgery, but also on the timing of blood collection. The spectrum of coagulopathy perioperatively includes those who may have a hypercoagulable state at one end and those who bleed due to coagulation factor deficiency.

Who are the patients who need thromboprophylaxis?

Surgical patients are at risk of developing venous thromboembolism. It is, however, important to recognize that there exist both definable operative procedures and definable groups of patients with significantly higher than normal rates of postoperative thromboembolism. It has been shown that, without prophylaxis, the incidence of deep vein thrombosis (DVT) is about 14% in gynaecological surgery, 22% in neurosurgery, 26% in abdominal surgery and 45–60% in orthopaedic surgery.[2] In patients with malignancy these rates are markedly higher. There are numerous patient-specific risk factors that also influence the individual risk of thrombosis. Despite this knowledge and the availability of effective prophylactic methods and consensus guidelines, thromboembolism remains an important problem in surgery. There is a low level of implementation of prophylaxis among clinicians and several surveys indicate that there is still considerable under-use of thromboprophylaxis, because of lack of awareness of the problem of thromboembolism combined with fears of bleeding complications and availability of cost-effectiveness of thromboprophylaxis. Patient-specific risk factors influencing the perioperative risk of thrombosis include history of thromboembolism, malignancy, age > 40 years, obesity, varicose veins, prolonged immobilisation, dehydration, heart failure, nephritic syndrome, stroke myeloproliferative syndrome, Becets disease, pregnancy and peuperium. Other factors include patients on drugs like oral contraceptives, hormone replacement therapy and those with inherited thrombophilias, namely, activated protein C resistance, antithrombin deficiency, protein S deficiency, hyperhomocystei-naemia and protrombin gene mutation G20210A. Some acquired thrombophilias posing risk of thrombosis include antiphospholipid antibody syndrome and sustained elevated factor FVII.A risk assessment model has been developed by the American college of chest physicians categorising the patients into very high, high, moderate and low risk.[3] (Table1).

What are the various regimens available?

Low-molecular weight heparin (LMWH) is the gold standard in surgical thromboprophylaxis. These are easy to use as a once-per-day injection without the necessity of monitoring. The greatest reduction in the risk of thrombosis has been found in patients with high-risk operations and risk factors. Although the currently available LMWHs, including certoparin, dalteparin, enoxaparin, nadroparin, tinzaparin and reviparin, differ in their pharmacokinetic properties, there is no evidence so far that any one of these products offers more or less protection from thromboembolism. Besides, none of the different LMWHs has been found to be especially useful or disadvantageous for specific patient groups (e.g. renal or liver insufficiency, heparin-induced thrombocytopenia). There are three prophylactic LMWH regimens in use in patients undergoing high-risk operations. In Europe, prophylaxis is traditionally started 12 h before surgery, whereas in North America it is initiated 12–48 h after surgery. The third regimen starts prophylaxis either more than 12 h before or 12 h after surgery. Thromboprophylaxis is started before surgery on the basis of previous observations that surgical interventions led to activation of coagulation, promoting the generation of thrombi.

New antithrombotic drugs under investigation that target novel sites in the coagulation pathway, include tissue-factor FVIIa, FVa, FVIIIa, FIXa, FXa, FXIIIa,PAI-1 and thrombin. One such new anticoagulant is fondaparinux, a synthetic molecule that is structurally and functionally like heparin, consisting of five saccharide units. Like heparin, it binds and activates antithrombin but inhibits only FXa and not thrombin. Trials in patients posted for major orthopaedic procedures have revealed that fondaparinux 2.5mg once daily, starting 6 h after surgery gives a clear benefit compared with enoxaparin, in reducing the incidence of venous thromboembolism. **[4]**Another new anticoagulant agent is ximelagatran, a non-covalent, synthetic, direct thrombin inhibitor. It is available in an oral preparation with very predictable and reproducible pharmacokinetic and pharmacodynamic profiles. Besides oral administration, ximelagatran has a number of benefits, including rapid onset of action, lack of drug–food interactions, and no requirement for routine blood coagulation monitoring.

Management of patients on oral anticoagulants

Perioperative management of patients on regular oral anticoagulants is guided by the risk of thromboembolism and the bleeding associated with different anticoagulant strategies [5].

While the risk of haemorrhage depends mainly on the site and type of surgery, the risk of thromboembolism depends on the indication for regular oral anticoagulation (arterial or venous prophylaxis), how long ago the patient had a thrombosis. In patients at high risk of thromboembolism, the anticoagulant-free window should be as short as possible, and during the time from stopping them to resuming coumarins an alternative anticoagulant should be given at a therapeutic or high prophylactic dose. Intravenous UFH is most useful as it can be given up to 2–4 h before surgery, can be easily monitored, and can be restarted soon after surgery with slowly increasing doses. LMWHs are less useful because of their long half-life and the limited possibility of antagonizing their anticoagulant

effect. In patients at low risk of thromboembolism, the oral anticoagulant-free window can be longer and an alternative anticoagulant, if necessary, can be given in prophylactic doses. In these cases, LMWHs may be preferred. Classification of patients into groups at high and low risk of thromboembolism (table2) is based mainly on the chronic and not necessarily perioperative risk of recurrence, and is somewhat arbitrary.[5] There is no strict rule as to when coumarins should be stopped before surgery, as this decision depends on several factors, including the degree of anticoagulation, the type of coumarin, the indication, the time between hospital admission and surgery, and whether UFH can be administered intravenously. Spontaneous normalization of the INR takes about 4 days before surgery in patients with an INR between 2 and 3 who are taking warfarin. VitaminK takes at least 24 hours to fully antagonize oral anticoagulation. If urgent reversal of oral anticoagulation is needed, treatment includes infusion of fresh frozen plasma (FFP) or prothrombin. Both FFP and prothrombin complex concentrate, lower INR values within minutes. Prothrombin complex concentrate, is however increasingly being used as it is more reliable and causes less volume overload. Recombinant, activated FVIIa (rFVIIa) can also lower INR values quickly and effectively. This treatment, however, should be considered only if severe bleeding occurs.

Thromboprophylaxis in patients undergoing regional anaesthesia

Neuraxial anaesthesia and analgesia provide excellent postoperative analgesia and allow early mobility after major surgery. The most feared complication of neuraxial anaesthesia is epidural haematoma, which has potentially devastating neurological complications. As number of patients treated with drugs interfering with blood coagulation or platelet function is on a rise, the anaesthetist is frequently faced with the problem of whether neuraxial anaesthesia is still an option or whether such co-medication means it is contraindicated. Several US and European societies have issued guidelines on locoregional anaesthesia in patients treated with heparin, oral anticoagulation, drugs interfering with platelet function, and other drugs used for thromboprophylaxis[6]. (table3) Contraindication to neuraxial block includes, prothrombin time (PT) INR>1.5, APTT >40 s and platelet count <50 000 ml/1.

Table 1

Low risk	Moderate risk	High risk	Very high risk
Uncomplicated minor surgery in patients <40 yr with no clinical risk factors	1)Major and minor surgery in patients 40–60 yr with no clinical risk factors 2)Major surgery in patients >40 yr who have additional risk factors 3)Minor surgery in patients with risk factors	Major surgery in patients <40 yr with no additional risk factors	1)Major surgery in patients >40 yr plus previous venous thromboembolic or malignant disease or hypercoagulable state 2)Elective major orthopaedic surgery or hip fracture or stroke or spinal cord injury or multiple trauma

Risk assessment models can be easily implemented in daily routine and produce greater awareness about thromboprophylaxis and a greater sense of security among anaesthetists and surgeons.

Table 2

	Risk factors	Regimens
Low risk	No history of thromboembolism. Last venous thromboembolic episode >3 months. Last arterial thromboembolic event >1 month. Mechanical heart valve without previous thromboembolic event. No permanent patient-specific risk factors (e.g. cancer, thrombophilia, immobilization etc.)	Preoperative: Stop coumarins 3–5 days before surgery. If INR<2 start LMWH or UFH at prophylactic doses until surgery (time between last heparin injection and surgery depends on dose and type of heparin) Postoperative:Give LMWH or UFH starting 12–24 h after surgery at prophylactic doses until INR>2.Start coumarins within 24–48 h after surgery
High risk	Last venous thromboembolic episode <3 months. Last arterial thromboembolic event <1 month. Mechanical heart valve with previous thromboembolic events. Atrial fibrillation. Permanent patient-specific risk factors (e.g. cancer, thrombophilia, immobilization etc.)	Preoperative: Stop coumarins 3–5 days before surgery. If INR<2 start UFH i.v. at therapeutic doses until 4–6 h before surgery. Alternatively,LMWH can be given at therapeutic doses; last injection must be >24 h before surgery Postoperative: 8–12 h after surgery start UFH i.v. (or LMWH s.c.) at increasing doses until therapeutic level is reached, continue until INR>2. Start coumarins within 24–48 h after surgery

Table 3: Current recommendation for spinal/epidural Anaesthesia & Anticoagulants

Classification	Medications	Recommendations	Laboratory
Antiplatelet's	Aspirin/NSAIDS Ticlopidine Clopidogrel Abciximab Eptifibatide Triofoban	None Discontinue 14 days before Discontinue 7 days before Avoid	None None None None
Anticoagulants	Warfarin	Discontinue 4 ~ 5 days before Monitor patient for 24 hr post spinal, epidural or removal of catheter	PT/INR prior to needle placement or catheter removal; INR < 1.5
Heparin	Subq heparin	Delay until after block	>4 days check platelet count
	IV heparin	Delay until 1 hr after block; remove catheter 2~4 hr after last dose	Measure PTT
LMWH	Ardeparin Dalteparin Enoxaparin Tinzaparin Danaparoid	Preop: block 10~12 hrs after last dose; high dose delay 24 hrs. Postop: Twice daily dose delay 1st dose for 24 hrs; 2 hr delay after catheter removal. Once daily dose 1st dose 6~8 hrs postop; remove catheter 10~12 hrs after last dose and wait 2 hrs until next dose.	None
Herbal Preparations	Garlic Ginkgo Ginseng Ginger Feverfew Vitamin E	Discontinue 5~7 days before surgery	None
New Anticoagulants	Bivalirudin Lepirudin Fondaparinux	Unknown; assess risk Extreme caution; atraumatic needle placement; no catheters	None

Perioperative hemorrhage

Besides the fact that patients may bleed due to the surgical procedure or inability to establish haemostasis, it is difficult to predict which patients will bleed using routine tests like bleeding time, platelet count, PT,aTTP or even even newer ones like platelet function analysers. Thromboelastography is of some value.The best judge is probably history and clinical examination. Surgery or major trauma is the ultimate test of the haemostatic system. Patients who have never bled to any significant degree can bleed excessively during surgery. Rapid and appropriate diagnostics to detect a possible underlying haemostatic defect, either inherited or acquired, are of pre-eminent importance. A haemostatic defect should always be considered if bleeding occurs simultaneously at multiple sites, presents as slow oozing from a non-identifiable source, or is delayed after initially adequate haemostasis. Bleeding from a single site or sudden onset of massive bleeding is probably due to a local structural defect. Assessment of a patient with a suspected coagulation defect should always include a thorough re-evaluation of his or her history, determination of any drugs given before surgery, including crystalloids, colloids and blood products, and a physical examination to determine the type and location of the bleeding. Initial laboratory evaluation should cover the entire range of possible coagulation defects, including clotting factor deficiencies, thrombocytopenia (and if possible thrombocytopathia), hyperfibrinolysis, and disseminated intravascular coagulation (DIC).

Component Therapy

Anaesthetists and oncologists have issued guidelines for platelet transfusion. [7] According to these guidelines, prophylactic platelet transfusions are indicated in leukaemia patients, at platelet counts <10, 000 /µ1 in the absence of fever, heparin treatment or active minor bleeding. For major surgery, platelet transfusions are recommended to maintain platelet counts above 50, 000 / µl, particularly if microvascular bleeding occurs. Minor surgery, however, can be performed without platelet transfusion in patients with a platelet count <50, 000/ µ1. In certain situations in which platelet dysfunction may be present, as after cardiopulmonary bypass, and when the consequences of bleeding might be dertrimental such as in neurosurgery, maintaining platelet counts between 50, 000 and 1,00,000/µ1may be necessary. Only with severe platelet dysfunction will platelet counts>1, 00,000/µ1 require transfusion. Transfusion of FFP is considered to be indicated for urgent reversal of anticoagulation induced by vitamin K antagonists (besides the use of prothrombin complex concentrates), bleeding in the presence of an

elevated PT (INR >1.6) or aPTT (>1.5 times normal) and in those patients transfused with >1 blood volume when PT and aPTT are unavailable.[8] FFP transfusions should not be given as volume replacement. Red blood cell transfusions have also been advocated to improve blood coagulation. It is unlikely; however, that reduction of the haematocrit alone compromises blood coagulation significantly. Decreasing the haematocrit gradually from 40%to 10%, thereby maintaining platelet count and coagulation factors at normal levels, does not compromise blood coagulation in any way, as assessed by thrombelastography.

Factor concentrates replacement and drug therapy for bleeding disorders

Inherited bleeding disorders: These disorders may involve the platelet function, plasma mediators of hemostasis or fibrinolytic pathways.Von Willebrand disease may involve quantitative or qualitative deficiency of vWF.The factor is responsible for platelet adhesion to the extracellular matrix and acts as a carrier molecule to prevent proteolytic degradation of factor VIII in free plasma. Easy bruising, recurrent epistaxis, menorrhagia and sometimes serious spontaneous haemorrhage like haemarthrosis, prolonged aPTT, bleeding time, reduced platelet aggregation and vWF concentration. The PFA-100 test has now replaced bleeding time. Treatment includes desmopressin acetate (DDAVP), specific factor vWF and factorVIII concentrate. Hemophilia, a relatively uncommon disorder with diverse clinical features, generally presents as spontaneous hemorrhage involving the joints or deep muscles. However mild cases of HemophiliaA may not be identified until later in life, often after unexplained bleeding with surgery or trauma. A prolonged aPTT with normal PT and bleeding time are suggestive of the disease. Specific factor VIIIc measure is a confirmatory.Desmopressin in mild cases and administration of recombinant or purified factor VIII concentrates,prothrombin complex concentrates or recombinant factor VII may help.[9]HemophiliaB(Christmas disease) necessitates replacement with factor IX concentrates.

Acquired bleeding disorders: Drugs and disease both can contribute to perioperative bleeding [10,11] (table4,5) [11]

Table 4: Anticoagulant Agents

Drug	Site of Action	Route	Plasma Half-life	Excretion	Antidote	Stop before Procedure	Prolongation of PT/aPTT
Unfractionated heparin	IIa/Xa	IV/SC	1.5 hr	Hepatic	Protamine	6 hr	No/Yes
LMWH	Xa	SC	4.5 hr	Renal	Protamine (partial reversal)	12-24 hr	No/No
Streptokinase	Plg	IV	23 min	Hepatic	Antifibrinolytics	3 hr	Yes/Yes
t-PA	Plg	IV	<5 min	Hepatic	Antifibrinolytics	1 hr	Yes/Yes
Warfarin	Vitamin K–dependent factors	Oral	2-4 days	Hepatic	Vitamin K rfVIIa PCCs Plasma	2-4 days	Yes/No

Table 5: Antiplatelet Agents

Drug	Site of Action	Route	Plasma Half-life	Metabolism	Antidote	Stop before Procedure	Prolongation of PT/aPTT
Aspirin	COX 1-2	Oral	20 min	Hepatic	None	7 days	No/No
Dipyridamole	Adenosine	Oral	40 min	Hepatic	None	24 hr	No/No
Clopidogrel	ADP	Oral	7 hr	Hepatic	None	5 days	No/No
Ticlopidine	ADP	Oral	4 days	Hepatic	None	10 days	No/No
Abciximab	GPIIb-IIIa	IV	30 min	Renal	None	72 hr	No/No
Eptifibatide	GPIIb-IIIa	IV	2.5 hr	Renal	None	24 hr	No/No
Tirofiban	GPIIb-IIIa	IV	2 hr	Renal	Hemodialysis	24 hr	No/No

Table 6

Drug	Therapy
Dabigatran-factor IIa inhibitor	1.<2hours of ingestion -activated charcoal 2.If renal function impaired consider hemodialysis 3.Activated prothrombin complex concentrates(aPCC)-50U/kg I/V maximum upto 5000U 4.Recombinant factor VIIa 5.Future-aDabi-Fab, PER977
Apixaban, Rivaroxaban-factorXa inhibitor	1.<2hours of ingestion -activated charcoal 2.3- factor prothrombin complex concentrates(3-PCC) 3.4 factor-PCC-50U/kg I/V 4.Recombinant factor VIIa 5.Future-PRT4445(modified recombinant factor Xa),PER977
Argatroban, Bivalirudin, Lepirudin -Direct Thrombin Inhibitors (DTIs)	1.Fresh frozen plasma 2.4 factor-PCC
Aspirin, Clopidogrel, Prasugrel	1.Platelet transfusion 2.Desmopressin

Liver Disease: Severe liver disease impairs synthesis of coagulation factors, impedes clearance of activated clotting and fibrinolytic proteins, and produces quantitative and qualitative platelet dysfunction. Laboratory findings commonly associated with liver disease include a prolonged PT, possible prolongation of the aPTT, and thrombocytopenia. Prolongation of bleeding time reflects qualitative defects in platelet adhesion and aggregation. Treatment of bleeding is based on laboratory abnormalities. Plasma and platelets frequently are administered for acute bleeding. Low fibrinogen concentrations may necessitate cryoprecipitate administration or antifibrinolytic drugs.

Renal Disease: Platelet dysfunction is common in chronic renal failure, as reflected by a prolonged bleeding time and propensity for bleeding associated with surgery or trauma. Underlying mechanisms appear multifactorial and may include accumulation of guanidinosuccinic acid and nitric oxide in uremic plasma. Red blood cell concentrate infusion for correction of anaemia results in shortened bleeding times, probably due to the role of red blood cells in causing platelet margination along the vessel wall under laminar flow conditions. Both dialysis and correction of anemia have been reported to shorten bleeding times in these patients. Cryoprecipitate, desmopressin (0.3 µg/kg) and conjugated estrogens may help.

Disseminated intravascular coagulation: Disseminated intravascular coagulation (DIC) comprises a pathophysiologic hemostatic response to tissue factor/factor VIIa complex exposure and activation of the extrinsic pathway of coagulation. Precipitating factors including trauma, amniotic fluid embolus, malignancy, sepsis, or incompatible blood transfusions. DIC presents clinically as a diffuse bleeding disorder associated with consumption of coagulation factors and platelets during widespread microvascular thrombotic activity. There is underlying fibrinolysis, providing a counterregulatory mechanism to maintain vascular integrity. Laboratory findings include reductions in platelet count, prolongation of the PT, aPTT, and thrombin time (TT), and elevated concentrations of soluble fibrin and fibrinogen degradation products. Management of DIC includes treatment of the underlying condition precipitating hemostatic activation and selective blood component transfusions to replete coagulation factors and platelets. Antifibrinolytic therapy is avoided owing to potential for catastrophic thrombotic complications.

Reversal of newer oral anticoagulants and antiplatelet agents in emergency situations

Newer anticoagulants are more effective and have shorter half lives than the older warfarin and are been used increasingly in patients needing thromboprophylaxis .However, what can be done when these patients come for emergency surgery and are bleeding profusely is an anaesthesiologist's nightmare as there is no specific antidote to reverse these drugs. The routine coagulation assays are not reliable measures for the effect of these drugs. Besides supportive therapy and investigating the cause, the following therapy has been suggested. [12, 13, 14] (Table 6)

rFVIIa

Although not yet approved for indications other than bleeding in haemophiliacs with antibodies, rFVIIa may be the ultimate haemostatic drug. rFVIIa is so far the only haemostatic drug that not only replaces a missing factor but actively initiates and promotes the coagulation process. The haemostatic effect of rFVIIa depends on its property of binding to TF and activated platelets, thereby rapidly activating

FII to thrombin and FX to FXa respectively.[15] The result is a local thrombin burst that enables feedback activation of intrinsic coagulation factors, the activation of more platelets, and finally the generation of fibrin. A major advantage of rFVIIa is that this procoagulant effect does not occur systemically in the circulation but is limited to the site where the vessel is injured. rFVIIa has been used successfully in patients with coumarin-induced bleeding, upper gastrointestinal bleeding, severe thrombocytopenia and thrombocytopathia and in patients with severe haemorrhage from trauma, neurosurgery, cardiac surgery and obstetric surgery.

Emerging challenges

A challenging and growing problem in surgery is the increased use of new, non-antagonizable anticoagulants such as fondaparinux, ximelagatran and recombinant nematode anticoagulant protein c2 (NAPc2), a FVIIa-TF inhibitor. Use of rFVIIa in these clinical situations is not clear and its high cost is a definite constrain. Another non-antagonizable anticoagulant is recombinant activated protein which is currently approved only in patients with severe sepsis. Although situations where patients receiving this drug need surgery may occur only rarely, their management will be challenging. In cases of bleeding, the infusion should be stopped immediately. As there is no known antidote administration of rFVIIa could theoretically be considered.

CONCLUSION

Perioperative coagulopathy impacts on patient outcome by influencing final blood loss and transfusion requirements. The recognition of pre-existing disturbances and the basic understanding of the principles and dynamic changes of haemostasis during surgery are pre-conditions for safe patient management.

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