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GUIDELINES

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

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The aims of severe perioperative bleeding management are three-fold. First, preoperative identification by anamesis and laboratory testing of those patients for whom the perioperative bleeding risk may be increased. Second, implementation of strategies for correcting preoperative anaemia and stabilisation of the macro- and microcirculations in order to optimise the patient's tolerance to bleeding. Third, targeted procoagulant interventions to reduce the amount of bleeding, morbidity, mortality and costs. The purpose of these guidelines is to provide an overview of current knowledge on the subject with an assessment of the quality of the evidence in order to allow anaesthetists throughout Europe to integrate this knowledge into daily patient care wherever possible. The Guidelines Committee of the European Society of Anaesthesiology (ESA) formed a task force with members of scientific subcommittees and individual expert members of the ESA. Electronic databases were searched without language restrictions from the year 2000 until 2012. These searches produced 20 664 abstracts. Relevant systematic reviews with meta-analyses, randomised controlled trials, cohort studies, case-control studies and cross-sectional surveys were selected. At the suggestion of the ESA Guideline Committee, the Scottish Intercollegiate Guidelines Network (SIGN) grading system was initially used to assess the level of evidence and to grade recommendations. During the process of guideline development, the official position of the ESA changed to favour the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. This report includes general recommendations as well as specific recommendations in various fields of surgical interventions. The final draft guideline was posted on the ESA website for four weeks and the link was sent to all ESA members. Comments were collated and the guidelines amended as appropriate. When the final draft was complete, the Guidelines Committee and ESA Board ratified the guidelines.

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Contents

1 ABBREVIATIONS

A5, A10	Amplitude at 5/10 min following clotting time
AAGBI	Association of Anaesthetists of Great Britain and Ireland
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
ALI	Acute lung injury
APA	Anti-platelet agents
APCC	Activated prothrombin complex concentrate
APTEM	Thromboelastometry assay incorporating aprotinin and recombinant tissue factor as an activation enhancer
aPTT	Activated partial thromboplastin time

AT	Antithrombin
ATP	Adenosine triphosphate
AVB	Acute variceal bleeding
BART	Blood conservation using antifibrinolytics in a randomised trial
BAT	Bleeding assessment tool
CABG	Coronary artery bypass graft
CADP	Collagen and ADP (PFA-100 assay)
CCI	Corrected count increment
CEPI	Collagen and epinephrine (PFA-100 assay)
CFT	Clot formation time (also called k time)
CI	Confidence interval
CKD	Chronic kidney disease
CLD	Chronic liver disease
CMV	Cytomegalovirus
COX	Cyclo-oxygenase
CPA	Cone and plate(let) analyser (Impact-R)
CPB	Cardiopulmonary bypass
CT	Clotting time
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
DPG	Diphosphoglycerol
EACA	ε-aminocaproic acid
EMA	European Medicines Agency
EXTEM	Extrinsic thromboelastometry assay incorporating recombinant tissue factor as activation enhancer
FF	Functional fibrinogen (assay)
FFP	Fresh frozen plasma
FIBTEM	Fibrinogen thromboelastometry assay, incorporating recombinant tissue factor as activation enhancer and cytochalasin D as platelet inhibitor
FNHTR	Febrile non-haemolytic transfusion reactions
FVIII	Factor VIII
FXa	Factor Xa
FXIII	Factor XIII
G	Clot rigidity
GP	Glycoprotein
Hb	Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HELLP	Haemolysis, elevated liver enzymes and low platelets
HEPTEM	Thrombelastometry assay incorporating heparinase and ellagic acid as an activation enhancer
HES	Hydroxyethyl starch
HIV	Human immunodeficiency virus
HTLV	Human T-cell lymphotropic virus
HTRs	Haemolytic transfusion reactions
HV	Hyperoxic ventilation
ICH	Intracerebral haemorrhage
ICS	Intraoperative cell salvage
ICT	Intracardiac thrombi
ICU	Intensive care unit
INR	International normalised ratio
INTEM	Intrinsic thromboelastometry assay incorporating ellagic acid as activation enhancer
LI30	Lysis index (% of clot strength remaining 30 min after CT)
LMWH	Low molecular weight heparin
LTA	Light transmittance aggregometry
LY30	Lysis index (% of clot strength remaining 30 min after MA)
MA	Maximum amplitude
MBD	Mild bleeding disorders
MCB	Mucocutaneous bleeding

MCE	Maximum clot elasticity
MCF	Maximum clot firmness
MEA	Multiple electrode aggregometry (Multiplate)
ML	Maximum lysis
NATEM	Native thromboelastometry assay (no activation enhancement or additional modifications)
NICE	National Institute of Health and Clinical Excellence
NOA	New oral anticoagulant agent
NSAID	Non-selective, non-steroidal anti-inflammatory drug
OLT	Orthotopic liver transplantation
PAI	Plasminogen activator inhibitor
paO2	Partial pressure of oxygen
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PEP	Pulmonary embolism prevention (trial)
PFA-100	Platelet function analyser
PPV	Pulse pressure variation
PT	Prothrombin time
r	Reaction time
RBC	Red blood cell
RBD	Rare bleeding disorder
RCT	Randomised controlled trial
rFVIIa	Recombinant activated factor VII
ROTEM	Thromboelastometry
SBT	Skin bleeding time
ScvO2	Central venous oxygen saturation
SD	Solvent and detergent
SHOT	Serious hazards of transfusion
SIGN	Scottish Intercollegiate Guidelines Network
SLT	Standard laboratory test
SPRINT	Systolic blood pressure intervention trial
SSRI	Selective serotonin reuptake inhibitors
SVV	Stroke volume variation
TACO	Transfusion-associated circulatory overload
TAE	Transcatheter arterial embolisation
TA-GVHD	Transfusion-associated graft-versus-host disease
TEG	Thromboelastometry
TF	Tissue factor
THA	Total hip arthroplasty
TRALI	Transfusion-related acute lung injury
TRAP	Thrombin receptor activator peptide
TRICC	Transfusion requirements in critical care (trial)
TRIM	Transfusion-related immunomodulation
UFH	Unfractionated heparin
UGIB	Upper gastrointestinal bleeding
vCJD	Variant Creutzfeldt-Jacob disease
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
VWD	Von Willebrand disease
VWF	Von Willebrand factor

2 SUMMARY: RECOMMENDATIONS, SUGGESTIONS AND STATEMENTS

Grade of recommendation shown in bold type (see Table 1)

Evaluation of coagulation status

We recommend the use of a structured patient interview or questionnaire before surgery or invasive procedures, which considers clinical and family bleeding history and detailed information on the patient's medication. **1C**

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery. **1C**

We recommend the application of transfusion algorithms incorporating predefined intervention triggers to guide haemostatic intervention during intraoperative bleeding. **1B**

We recommend the application of transfusion algorithms incorporating predefined intervention triggers based on point-of-care (POC) coagulation monitoring assays to guide haemostatic intervention during cardiovascular surgery. **1C**

Evaluation of platelet function

We suggest preoperative platelet function testing only in addition to a positive bleeding anamnesis. **2C**

We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions and antiplatelet medication. **2C**

Preoperative correction of anaemia

We recommend that patients at risk of bleeding are assessed for anaemia 4–8 weeks before surgery. **1C**

If anaemia is present, we recommend identifying the cause (iron deficiency, renal deficiency or inflammation). **1C**

We recommend treating iron deficiency with iron supplementation (oral or intravenous). **1B**

If iron deficiency has been ruled out, we suggest treating anaemic patients with erythropoietin-stimulating agents. **2A**

If autologous blood donation is performed, we suggest treatment with erythropoietin-stimulating agents in order to avoid preoperative anaemia and increased overall transfusion rates. **2B**

Optimising macrocirculation

We recommend aggressive and timely stabilisation of cardiac preload throughout the surgical procedure, as this appears beneficial to the patient. **1B**

Table 1 Grades of recommendation – GRADE system

		Clarity of risk/benefit	Quality of supporting evidence	Implications
1A	**Strong recommendation. High quality evidence.**	Benefits clearly outweigh risk and burdens, or vice versa.	Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Strong recommendation, can apply to most patients in most circumstances without reservation.
1B	**Strong recommendation. Moderate quality evidence.**	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation, likely to apply to most patients
1C	**Strong recommendation. Low quality evidence.**	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.	Relatively strong recommendation; might change when higher quality evidence becomes available
2A	**Weak recommendation. High quality evidence.**	Benefits closely balanced with risks and burdens.	Consistent evidence from well performed, randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values.
2B	**Weak recommendation. Moderate quality evidence.**	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
2C	**Weak recommendation. Low quality evidence.**	Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable

We recommend the avoidance of hypervolaemia with crystalloids or colloids to a level exceeding the interstitial space in steady state, and beyond an optimal cardiac preload. **1B**

We recommend against the use of central venous pressure and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimise preload during severe bleeding; dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead. **1B**

We suggest the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol-based manner. **2C**

Compared with crystalloids, haemodynamic stabilisation with iso-oncotic colloids, such as human albumin and hydroxyethyl starch, causes less tissue oedema. **C**

We suggest the use of balanced solutions for crystalloids and as a basic solute for iso-oncotic preparations. **2C**

Transfusion triggers

We recommend a target haemoglobin concentration of 7–9 $g\,dl^{-1}$ during active bleeding. **1C**

Oxygen fraction

We recommend that inspiratory oxygen fraction should be high enough to prevent arterial hypoxaemia in bleeding patients, while avoiding extensive hyperoxia ($PaO_2 > 26.7$ kPa [200 mmHg]). **1C**

Monitoring tissue perfusion

We recommend repeated measurements of a combination of haematocrit/haemoglobin, serum lactate, and base deficit in order to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. These parameters can be extended by measurement of cardiac output, dynamic parameters of volume status (e.g. stroke volume variation, pulse pressure variation) and central venous oxygen saturation. **1C**

Transfusion of labile blood products

We recommend that all countries implement national haemovigilance quality systems. **1C**

We recommend a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products. **1A**

We recommend photochemical pathogen inactivation with amotosalen and UVA light for platelets. **1C**

We recommend that labile blood components used for transfusion are leukodepleted. **1B**

We recommend that blood services implement standard operating procedures for patient identification and that staff be trained in early recognition of, and prompt response to, transfusion reactions. **1C**

We recommend that multiparous women be excluded from donating blood for the preparation of FFP and for the suspension of platelets in order to reduce the incidence of transfusion-related acute lung injury. **1C**

We recommend that all RBC, platelet and granulocyte donations from first-or second-degree relatives be irradiated even if the recipient is immunocompetent, and all RBC, platelet and that granulocyte products be irradiated before transfusing to at-risk patients. **1C**

We recommend the transfusion of leukocyte-reduced RBC components for cardiac surgery patients. **1A**

Cell salvage

We recommend the routine use of red cell salvage which is helpful for blood conservation in cardiac operations using CPB. **1A**

We recommend against the routine use of intraoperative platelet-rich plasmapheresis for blood conservation during cardiac operations using CPB. **1A**

We recommend the use of red cell salvage in major orthopaedic surgery because it is useful in reducing exposure to allogeneic red blood cell transfusion. **1A**

We recommend that intraoperative cell salvage is not contraindicated in bowel surgery, provided that initial evacuation of soiled abdominal contents and additional cell washing are performed, and that broad-spectrum antibiotics are used. **1C**

Storage lesions

We recommend that RBCs up to 42 days old should be transfused according to the first-in first-out method in, the blood services to minimise wastage of erythrocytes. **1C**

Coagulation management

We recommend treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen concentrations or function. **1C**

We recommend that a plasma fibrinogen concentration <1.5–2.0 $g\,l^{-1}$ or ROTEM/TEG signs of functional fibrinogen deficit should be triggers for fibrinogen substitution. **1C**

We suggest an initial fibrinogen concentrate dose of 25–50 $mg\,kg^{-1}$. **2C**

We suggest that the indication for cryoprecipitate is lack of available fibrinogen concentrate for the treatment of bleeding and hypofibrinogenaemia. **2C**

In cases of ongoing or diffuse bleeding and low clot strength despite adequate fibrinogen concentrations, it is likely that FXIII activity is critically reduced. In cases of significant FXIII deficiency (i.e. <60% activity), we suggest that FXIII concentrate (30 IU kg^{-1}) can be administered. **2C**

We recommend that patients on oral anticoagulant therapy should be given prothrombin complex concentrate (PCC) and vitamin K before any other coagulation management steps for severe perioperative bleeding. **1B**

We suggest that PCC (20–30 IU kg^{-1}) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients. **2C**

We suggest that off-label administration of recombinant activated factor VII (rFVIIa) can be considered for bleeding which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails. **2C**

Antifibrinolytics and tranexamic acid

We recommend the consideration of tranexamic acid (20–25 mg kg^{-1}). **1A**

We suggest the use of DDAVP under specific conditions (acquired von Willebrand syndrome). There is no convincing evidence that DDAVP minimises perioperative bleeding or perioperative allogeneic blood transfusion in patients without a congenital bleeding disorder. **2B**

Correction of confounding factors

We recommend maintaining perioperative normothermia because it reduces blood loss and transfusion requirements. **1B**

We suggest that rFVIIa may be used in treatment of patients with hypothermic coagulopathy. **2C**

While pH correction alone cannot immediately correct acidosis-induced coagulopathy, we recommend that pH correction should be pursued during treatment of acidotic coagulopathy. **1C**

We recommend that rFVIIa should only be considered alongside pH correction. **1C**

We suggest that calcium should be administered during massive transfusion if Ca^{2+} concentration is low, in order to preserve normocalcaemia ($\geq$0.9 mmol l^{-1}). **2B**

Emergency radiological/surgical interventions to reduce blood loss

We suggest that endovascular embolisation is a safe alternative to open surgical intervention after failed endoscopic treatment for upper gastrointestinal bleeding. **2C**

We suggest super-selective embolisation as primary therapy for treatment of angiogram positive lower gastrointestinal bleeding. **2C**

We suggest embolisation as first-line therapy for arterial complications in pancreatitis. **2C**

Cost implications

Bleeding and transfusion of allogeneic blood products independently increase morbidity, mortality, length of stay in ICU and hospital, and costs. **B**

Lysine analogues (tranexamic acid and ε-aminocaproic acid; EACA) reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several settings of major surgery and trauma. **A**

We recommend restricting the use of rFVIIa to its licensed indication because, outside these indications, the effectiveness of rFVIIa to reduce transfusion requirements and mortality remains unproven and the risk of arterial thromboembolic events as well as costs are high. **1A**

Cell salvage can be cost-effective**. A**

The cost-effectiveness of a formula-driven transfusion protocol has not been investigated.

Implementation of transfusion and coagulation management algorithms (based on ROTEM/TEG) can reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. **B**

Goal-directed therapy with coagulation factor concentrates (fibrinogen and/or PCC) may reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. **B**

Thromboembolic events are associated with increased in-hospital and post-hospital costs. **B**

Targeted therapy with fibrinogen and/or PCC guided by ROTEM/TEG is not associated with an increased incidence of thromboembolic events. **C**

Algorithms in specific clinical fields

Cardiovascular surgery

Withdrawal of aspirin therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. **A**

Withdrawal of clopidogrel therapy increases the risk of thrombosis; continuation of clopidogrel therapy increases the risk of bleeding. **A**

We recommend that a prophylactic dose of low molecular weight heparin should be administered subcutaneously 8–12 h before elective CABG surgery. This intervention does not increase the risk of perioperative bleeding. **1B**

We recommend that tranexamic acid or EACA should be considered before CABG surgery. **1A**

We suggest considering prophylactic preoperative infusion of 2 g fibrinogen concentrate in patients with fibrinogen concentration <3.8 g/L, because it may reduce bleeding following elective CABG surgery. **2C**

Prothrombin complex concentrate is effective for rapid reversal of oral anticoagulation before cardiac surgery. **A**

We recommend that intraoperative tranexamic acid or EACA administration should be considered to reduce perioperative bleeding in high-, medium- and low-risk cardiovascular surgery. **1A**

We recommend that tranexamic acid should be applied topically to the chest cavity to reduce postoperative blood loss following CABG surgery. **1C**

We recommend that fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiovascular surgery. **1B**

We suggest that recombinant FVIIa may be considered for patients with intractable bleeding during cardiovascular surgery once conventional haemostatic options have been exhausted. **2B**

We suggest that antiplatelet therapy with aspirin or clopidogrel may be administered in the early postoperative period without increasing the risk of postoperative bleeding. **2C**

We suggest that rFVIIa may be considered for patients with intractable bleeding after cardiovascular surgery once conventional haemostatic options have been exhausted. **2B**

We recommend the use of standardised haemostatic algorithms with predefined intervention triggers. **1A**

Gynaecological (non-pregnant) bleeding

We suggest against normovolaemic haemodilution because it does not reduce allogeneic transfusion. **2A**

Cell salvage may reduce allogeneic transfusion in gynaecological (including oncological) surgery. **C**

We suggest using preoperative intravenous iron to reduce allogeneic transfusion requirements in gynaecological cancer patients receiving chemotherapy. **2B**

We suggest using intravenous iron to correct preoperative anaemia in women with menorrhagia. **2B**

Preoperative fibrinogen and D-dimer evaluation in gynaecological cancer patients provide little useful information. **C**

Postoperative FFP transfusion is associated with an increased risk of venous thromboembolism in malignant gynaecological surgery. **C**

rFVIIa increases thromboembolic risk and has not been shown to reduce mortality. **B**

Tranexamic acid reduces the frequency of late bleeding after cone biopsy of the cervix. **B**

Tranexamic acid reduces perioperative bleeding in gynaecological cancer surgery. **C**

We suggest against the use of tranexamic acid in benign gynaecological operations such as myomectomy. **2B**

Obstetric bleeding

We recommend that peripartum haemorrhage should be managed by a multidisciplinary team. An escalating management protocol including uterotonic drugs, surgical and/or endovascular interventions, and procoagulant drugs should be available. **1C**

Risk awareness and early recognition of severe haemorrhage are essential. **C**

We suggest that patients with known placenta accreta are treated by multidisciplinary care teams. **2C**

Cell salvage is well tolerated in obstetric settings, provided that precautions are taken against rhesus isoimmunisation. **C**

We suggest that using perioperative cell salvage during caesarean section may decrease postoperative homologous transfusion and reduce hospital stay. **2B**

We recommend that moderate ($<9.5\,g\,dl^{-1}$) to severe ($<8.5\,g\,dl^{-1}$) postpartum anaemia be treated with intravenous iron rather than oral therapy. **1B**

Intravenous iron supplementation improves fatigue at 4, 8 and 12 weeks postpartum. **B**

Insufficient evidence exists to support the transfusion-sparing effect of intravenous iron supplementation.

We suggest that treatment with erythropoietin may correct anaemia more rapidly than treatment with folic acid and iron. **2C**

We suggest assessing fibrinogen concentration in parturients with bleeding, as concentrations $<2\,g\,l^{-1}$ may identify those at risk of severe PPH. **2C**

Platelet count $<100\times10^{9}\,l^{-1}$ at the onset of labour, particularly combined with plasma fibrinogen concentration $<2.9\,g\,l^{-1}$, may indicate an increased risk of PPH. **C**

aPTT and PT are of little predictive value for PPH. **C**

Thromboelastometry can identify obstetric coagulopathy and hyperfibrinolysis and guide haemostatic therapy. **C**

In life-threatening PPH, we suggest a transfusion protocol with a fixed product ratio or individualised procoagulant intervention and factor substitution. **2C**

Considering physiologically elevated fibrinogen concentrations in pregnancy, we suggest that a higher trigger value for treating hypofibrinogenaemia may be required. **C**

We recommend the administration of tranexamic acid in obstetric bleeding to reduce blood loss, bleeding duration and the number of units transfused. **1B**

We suggest that tranexamic acid be considered before caesarean section. **2C**

In antepartum bleeding, we suggest administration of tranexamic acid. **2B**

We recommend that rFVIIa should only be considered as last line therapy because of its thromboembolic risk. **1B**

We suggest that fibrinogen concentration and number of platelets should be optimised before administration of rFVIIa. **2C**

Orthopaedic surgery and neurosurgery

In elective orthopaedic surgery, we recommend the implementation of a blood transfusion protocol (algorithm), together with staff education. **1B**

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections. **B**

Infusion of colloids in patients with severe bleeding can aggravate dilutional coagulopathy by additional effects on fibrin polymerisation and platelet aggregation. **C**

We recommend that, for orthopaedic surgery, monotherapy with aspirin does not need to be discontinued. **1B**

We recommend discontinuing dual antiplatelet therapy before urgent intracranial neurosurgery. A risk-benefit analysis is required for the continuation of aspirin monotherapy during neurosurgery. **1B**

We recommend against performing orthopaedic surgery during the first three months after bare metal stent implantation or during the first twelve months after drug eluting stent implantation. **1C**

Preoperative medication with ADP-receptor antagonists or with new oral anticoagulants is associated with an increased risk of major bleeding and intracerebral haemorrhage (ICH), especially if used in combination. **B**

Reduced platelet activity is associated with early haematoma growth, more intraventricular haemorrhage and worse three-month outcome following ICH. **C**

Low platelet count, low plasma fibrinogen concentration and FXIII deficiency are predictive of bleeding complications in ICH, intracranial surgery and major spine surgery, particularly when they occur in combination. **C**

Preoperative measurement of plasma fibrinogen concentration provides more information on bleeding volume and transfusion requirements than standard screening tests. **C**

We suggest the use of viscoelastic tests (ROTEM/TEG) for monitoring perioperative haemostasis in major orthopaedic surgery and neurosurgery. **2C**

The intensity of oral anticoagulation with warfarin measured by INR, shows a close correlation to the incidence and severity of bleeding complications, in particular with ICH. **C**

We suggest administering tranexamic acid in total hip arthroplasty, total knee arthroplasty, and major spine surgery. **2A**

Tranexamic acid may promote a hypercoagulable state for some patients (with pre-existing thromboembolic events, hip fracture surgery, cancer surgery, age over 60 years, women). Therefore, we suggest an individual risk-benefit analysis instead of its routine use in these clinical settings. **2A**

We suggest the use of rFVIIa in patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery. **2C**

Prophylactic use of rFVIIa does not reduce perioperative blood loss or transfusion in non-haemophiliac and non-coagulopathic patients undergoing major orthopaedic surgery or neurosurgery, and it may increase the incidence of thromboembolic events. We, therefore, recommend against the prophylactic use of rFVIIa in these clinical settings. **1B**

We recommend restricting off-label use of rFVIIa to patients with severe bleeding who are unresponsive to other haemostatic interventions. **1C**

In patients with INR > 1.5, with life-threatening bleeding or ICH, we recommend that four-factor PCCs ($20–40\,IU\,kg^{-1}$), supplemented with vitamin K (10 mg by slow intravenous infusion), should be used for rapid reversal of vitamin K-antagonists (VKA). **1C**

In patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery, we suggest using activated PCCs (e.g. FEIBA, FVIII inhibitor bypassing agents). **2C**

New oral anticoagulants, such as rivaroxaban and dabigatran, may increase surgical bleeding and ICH growth. We suggest that PCC, FEIBA or rFVIIa may be used as non-specific antagonists in life threatening bleeding or ICH. **2C**

Visceral and transplant surgery

Despite PT, aPTT and INR indicating coagulopathy in chronic liver disease (CLD), global coagulation tests (thrombin generation and TEG/ROTEM) suggest that haemostasis is balanced in stable CLD. **C**

Mild to moderate prolongation of the preoperative PT and INR do not predict bleeding in patients with CLD. **C**

We recommend against the use of FFP for pre-procedural correction of mild to moderately elevated INR. **1C**

We suggest a platelet count of $\leq 50\,000\ \mu l^{-1}$ as a threshold for platelet transfusion before liver biopsy. **2C**

PFA-100 is not predictive of bleeding risk in cirrhosis. **C**

Bleeding time is influenced by many variables and is not useful to stratify bleeding risk. **C**

We recommend that, in acute liver failure, moderately elevated INR should not be corrected before invasive procedures, with the exception of intracranial pressure monitor insertion. **1C**

Fluid restriction, phlebotomy, vasopressors and transfusion protocols may be associated with low transfusion rates during orthotopic liver transplantation (OLT). **C**

We recommend the use of perioperative coagulation monitoring using ROTEM/TEG for targeted management of coagulopathy. **1C**

Antifibrinolytic therapy reduces blood loss and transfusion requirements in liver transplantation. **B**

We recommend antifibrinolytic drugs for treatment of fibrinolysis (evident from microvascular oozing or TEG/ROTEM clot lysis measurement) and not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis post-reperfusion. **1C**

We recommend against rFVIIa for prophylaxis; rFVIIa should be used only as rescue therapy for uncontrolled bleeding. **1A**

Point of care platelet function tests may help to stratify risk and rationalise platelet transfusion in patients taking antiplatelet drugs. **C**

A low central venous pressure and restrictive fluid administration reduce bleeding during liver resection. **B**

We suggest that antifibrinolytic drugs should be considered in cirrhotic patients undergoing liver resection. **2C**

Acute upper gastrointestinal bleeding

We recommend that acute variceal bleeding should be managed by a multidisciplinary team. A specific multimodal protocol for upper gastrointestinal haemorrhage should be available. **1C**

We recommend that early treatment involves immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding and early interventional endoscopy. Antibiotics must be started on admission. **1A**

Tranexamic acid reduces mortality but not rebleeding. **B**

rFVIIa should be used only as rescue therapy; we recommend against its routine use. **1C**

Coagulopathy and renal disease

Point-of-care tests of platelet function and bleeding time provide no reliable platelet function assessment in uraemia and no prediction of bleeding in this setting. **C**

We suggest that conjugated oestrogen therapy should be used in uraemia. **2C**

We suggest that desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. **2C**

There is no evidence to support use of rFVIIa in this setting.

Paediatric surgery

We suggest the use of perioperative coagulation analysis using viscoelastic point-of-care monitoring (ROTEM/TEG) for timely detection of coagulation defects including dilutional coagulopathy and hyperfibrinolysis. **2C**

No clear recommendation can be made regarding the choice of perioperative fluid replacement in children. **C**

We suggest that a critical haemoglobin threshold of $8\,g\,dl^{-1}$ for RBC transfusion may be safe in severe paediatric perioperative bleeding. **2C**

We suggest that transfusion of platelet concentrates may be considered if platelet count is $<50\,000$–$100\,000\ \mu l^{-1}$. **2C**

No clear recommendation can be made regarding the indication and dosing of FFP transfusion in bleeding children, but severe side-effects have been reported. **C**

We suggest that fibrinogen concentrate (30–$50\,mg\,kg^{-1}$) or cryoprecipitate ($5\,ml\,kg^{-1}$) may be used to increase plasma fibrinogen concentrations above trigger values of 1.5–$2.0\,g\,l^{-1}$ or FIBTEM MCF $>$ 7 mm in bleeding children. **2C**

We suggest that FFP may be used if no other fibrinogen source is available. **2C**

Data for PCC in children are limited and no dose recommendation can be made. **C**

No recommendation on the use of FXIII concentrate in bleeding children can be made.

We recommend against the use of rFVIIa in children. **1C**

We suggest against the routine use of desmospressin in the absence of haemophilia A or mild von Willebrand disease. **2C**

We suggest that perioperative antifibrinolytic therapy should be used to reduce blood loss and transfusion requirements in cardiac and non-cardiac paediatric surgery. **2A**

Antiplatelet agents

We recommend that aspirin therapy should continue perioperatively in most surgical settings, especially cardiac surgery. **1C**

Where aspirin withdrawal is considered, we recommend a time interval of 5 days. **1C**

For intra- or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7×10^{11} [i.e. two standard concentrates] per 7 kg body weight in adults). **2C**

Clopidogrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 5 days**. 1C**

Prasugrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 7 days**. 1C**

We recommend that antiplatelet agent therapy should resume as soon as possible postoperatively to prevent platelet activation**. 1C**

We suggest that the first postoperative dose of clopidogrel or prasugrel should be given no later than 24 h after skin closure. We also suggest that this first dose should not be a loading dose. **2C**

We recommend postponement of elective surgery following coronary stenting (at least 6 to 12 weeks for bare metal stent and one year for drug-eluting stents). **1C**

We recommend that a multidisciplinary team meeting should decide on the perioperative use of antiplatelet agents in urgent and semi-urgent surgery. **1C**

We suggest that urgent or semi-urgent surgery should be performed under aspirin/clopidogrel or aspirin/prasugrel combination therapy if possible, or at least under aspirin alone. **2C**

We suggest that platelet transfusion should be considered (dose: 0.7×10^{11} [i.e. two standard concentrates] per 7 kg body weight in adults) in cases of intra- or postoperative bleeding clearly related to clopidogrel or prasugrel**. 2C**

According to pharmacological characteristics, we suggest that the management of ticagrelor may be comparable to clopidogrel (i.e. withdrawal interval of 5 days). **2C**

Platelet transfusion may be ineffective for treating bleeding clearly related to ticagrelor when given 12 h before. **2C**

Heparin

We recommend that severe bleeding associated with intravenous unfractionated heparin (UFH) should be treated with intravenous protamine at a dose of 1 mg per 100 IU UFH given in the preceding 2–3 h. **1A**

We suggest that severe bleeding associated with subcutaneous UFH unresponsive to intravenous protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of intravenous protamine, with dose guided by aPTT**. 2C**

We suggest that severe bleeding related to subcutaneous low molecular weight heparin (LMWH) should be treated with intravenous protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered. **2C**

We suggest that severe bleeding associated with subcutaneous LMWH and unresponsive to initial administration of protamine could be treated with a second dose of protamine (0.5 mg per 100 anti-FXa units of LMWH administered). **2C**

Fondaparinux

We suggest that the administration of rFVIIa could be considered to treat severe bleeding associated with subcutaneous administration of fondaparinux (off-label treatment). **2C**

Vitamin K antagonists

We recommend that vitamin K antagonists (VKAs) should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery (mainly anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in VKA treated patients. **1C**

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score ≤ 2, patients treated for > 3 months for a non-recurrent VTE) undergoing procedures requiring INR <1.5, VKA should be stopped 5 days before surgery. No bridging therapy is needed. Measure INR on the day before surgery and give 5 mg oral vitamin K if INR exceeds 1.5. **1C**

We recommend bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score > 2, patients with recurrent VTE treated for <3 months, patients with a mechanical valve). Day 5: last VKA dose; Day 4: no heparin; Days 3 and 2: therapeutic subcutaneous LMWH twice daily or subcutaneous UFH twice or thrice daily; Day 1: hospitalisation and INR measurement; Day 0: surgery**. 1C**

We recommend that for groups 1 and 2 above, VKAs should be restarted during the evening after the procedure. Subcutaneous LMWH should be given postoperatively until the target INR is observed in two measurements**. 1C**

We recommend that for group 3 above, heparin (UFH or LMWH) should be resumed 6–48 h after the procedure. VKA can restart when surgical haemostasis is achieved. **1C**

We recommend that, in VKA treated patients undergoing an emergency procedure or developing a bleeding complication, PCC (25 IU FIX kg^{-1}) should be given. **1B**

We recommend to assess creatinine clearance in patients receiving NOAs and being scheduled for surgery. **1B**

New oral anticoagulants

We suggest that new oral anticoagulant agents (NOAs) should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery, (mainly anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in NOA treated patients. **2C**

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score 2, patients treated for >3 months for a non-recurrent VTE) undergoing procedures requiring normal coagulation (normal diluted thrombin time or normal specific anti-FXa level), NOAs can be stopped 5 days before surgery. No bridging is needed. **1C**

In patients treated with rivaroxaban, apixaban, edoxaban and in patients treated with dabigatran in which creatinine clearance is higher than 50 ml min^{1}, we suggest bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score >2, patients with recurrent VTE treated for <3 months). Day 5: last NOA dose; Day 4: no heparin; Day 3: therapeutic dose of LMWH or UFH; Day 2: subcutaneous LMWH or UFH; Day 1: last injection of subcutaneous LMWH (in the morning, i.e. 24 h before the procedure) or subcutaneous UFH twice daily (i.e. last dose 12 h before the procedure), hospitalisation and measurement of diluted thrombin time or specific anti-FXa; Day 0: surgery. **2C**

In patients treated with dabigatran with a creatinine clearance between 30 and 50 ml min^{-1}, we suggest to stop NOAs 5 days before surgery with no bridging. **2C**

We suggest that for groups 2 and 3, heparin (UFH or LMWH) should be restarted 6–72 h after the procedure, taking the bleeding risk into account. NOAs may be resumed when surgical bleeding risk is under control. **2C**

Comorbidities involving haemostatic derangement

We suggest that patients with haemostatic derangements associated with systemic, metabolic and endocrine diseases should be managed perioperatively in collaboration with a haematologist. **2C**

We suggest that selective serotonin reuptake inhibitor (SSRI) treatment should not be routinely discontinued perioperatively. **2B**

We suggest individualised perioperative discontinuation of antiepileptic agents, such as valproic acid, which may increase bleeding. **2C**

We do not recommend discontinuation of Gingko biloba extracts. **1B**

Patients with congenital bleeding disorders

Von Willebrand disease

We suggest that if VWD is suspected preoperatively, the patient be referred to a haematologist for assessment and planning of the intervention. **2C**

We recommend the use of bleeding assessment tools for predicting the perioperative risk of bleeding. **1C**

We recommend that patients with VWD be managed perioperatively in collaboration with a haematologist. **1C**

We recommend desmopressin as a first-line treatment for minor bleeding/surgery in patients with VWD, after a trial testing. The regimen is specified by published guidelines. **1C**

We recommend replacement of VWF with plasma-derived products for major bleeding/surgery. Treatment regimens are specified by published guidelines. **1C**

We suggest that antifibrinolytic drugs be used as haemostatic adjuncts. Treatment regimens are specified by published guidelines. **2C**

We suggest that platelet transfusion may be used only in case of failure of other treatments. **2C**

Platelet defects

We suggest referring the patient to a haematologist for assessment and planning of the intervention if inherited platelet defects are suspected preoperatively. **2C**

We recommend the use of a bleeding assessment tool for predicting the perioperative risk of bleeding. **1C**

We recommend that patients with severe inherited platelet disorders should be managed perioperatively in collaboration with a haematologist. **1C**

We suggest preoperative haemostatic correction in patients with inherited platelet disorders. **2C**

We suggest desmopressin be used to prevent/control perioperative bleeding in patients with inherited platelet defects. **2C**

We suggest antifibrinolytic drugs be used as haemostatic adjuncts in procedures involving patients with inherited platelet defects. **2C**

We recommend that rFVIIa treatment should be considered in patients with Glanzmann thrombasthenia undergoing surgery. **1C**

We recommend against routine platelet transfusion in patients with inherited platelet disorders. **1C**

There is insufficient evidence to recommend a threshold for perioperative prophylactic platelet transfusion in thrombocytopenic patients. **C**

Haemophilia A and B

We recommend that haemophilia patients should be referred preoperatively to a haematologist for assessment/intervention. **1C**

We recommend that surgery in haemophilia patients should be performed in specialised centres with expertise in coagulation disorders. **1C**

We recommend adequate perioperative replacement therapy to ensure safe surgery in haemophilia patients. **1C**

We suggest that perioperative replacement therapy (target factor level and duration) in haemophilia patients follows published guidelines. **2C**

We recommend either recombinant products or plasma-derived concentrates for perioperative replacement therapy in haemophilia patients **1C**

We suggest that coagulation factors be given perioperatively by continuous infusion. **2C**

We suggest either rFVIIa or activated PCCs for haemophilia patients with inhibitors. **2C**

We suggest antifibrinolytic drugs as perioperative adjunct therapy in haemophilia patients. **2C**

We suggest individualised perioperative thromboprophylaxis in haemophilia patients. **2C**

Rare bleeding disorders

We recommend that patients with rare bleeding disorders should be referred preoperatively to a haematologist for assessment/intervention. **1C**

We recommend that surgery in patients with rare bleeding disorders should be carried out in consultation with a haematologist with experience in factor deficiencies. **1C**

There is insufficient data to recommend routine perioperative supplementation of deficient factors in patients with rare bleeding disorders. **C**

We suggest that rFVIIa be used in perioperative bleeding due to inherited FVII deficiency. **2C**

If rFVIIa is given to control perioperative bleeding in inherited FVII deficiency, we suggest lower doses than in haemophilia patients. **2C**

There is insufficient data to recommend rFVIIa in perioperative bleeding for patients with other rare bleeding disorders. **C**

There is insufficient data to recommend peri-procedural desmopressin or antifibrinolytic drugs in patients with mild rare bleeding disorders. **C**

3 INTRODUCTION

Healthcare professionals face an increasingly difficult task in keeping up to date with the evidence on perioperative transfusion strategies, as the number of studies published in this area has increased dramatically during the last 20 years. Within the last 10 years alone, more than 100 different medical journals have published relevant systematic reviews.[1] This not only reflects the complexities of transfusion medicine but also the development of alternatives to transfusion and the move towards evidence-based perioperative practice. Thus, it is imperative to update evidence-based transfusion guidelines for healthcare professionals and researchers.

Particularly urgent is the need to assess the mounting evidence in support of restrictive transfusion strategies as being not only safe but also potentially beneficial in terms of mortality, morbidity, postoperative outcomes and long-term survival in both cardiac and non-cardiac surgery patients.[2–9] This evidence is challenged by the widespread practice of perioperative allogeneic blood transfusion, especially in cardiac surgery, where 40–90% of patients receive blood transfusions, using approximately 10–15% of the national supply of blood.[10–14] There is also an urgent need to consider potential resource utilisation issues associated with aggressive use of blood products, as their preparation and storage are expensive.[15,16]

Growing evidence indicates that measures to support and monitor coagulation, such as antifibrinolytic drugs, point-of-care technologies (e.g. thrombelastography, thromboelastometry) and fluid therapy, are important for quality improvement and may offer alternative effective approaches for limiting blood transfusion and decreasing perioperative bleeding.[17–20] However, as many of the current indications for, and alternatives to, transfusion are not based on high quality evidence, there is a need for well designed and performed clinical trials, and high quality systematic reviews.[21] Many of the existing data are from retrospective studies (with their inherent shortcomings) and more randomised clinical trials are urgently needed.

This guideline by the European Society of Anaesthesiology (ESA) aims to provide an up-to-date review and synthesis of the evidence, with recommendations which may guide practitioners towards safe and cost-effective strategies for minimising severe non-traumatic perioperative bleeding and maximising blood conservation. Additionally, this guideline will identify knowledge gaps and new clinical questions which will guide the design of future clinical trials. Acknowledging the variation in transfusion practices across countries, hospitals, specialties and surgical procedures, concerted efforts will be needed for rapid implementation of this guideline, promotion of safe and appropriate transfusion, avoidance of unnecessary transfusion, discontinuation of potentially harmful practices and assessment of novel strategies.[22–27]

4 METHODS

4.1 Selection of task force

In June 2010, the ESA Guideline Committee, chaired by Andrew Smith, nominated the chairperson of the Subcommittee on Transfusion and Haemostasis, Sibylle Kozek-Langenecker, to coordinate the core group of the task force, consisting of the Subcommittee chairpersons Patrick Wouters (circulation), Cesar Santullano (intensive care medicine) and Eduardo de Robertis (resuscitation and emergency medicine), and Subcommittee members Arash Afshari (evidence based practice) and Klaus Görlinger (transfusion and haemostasis). The ESA Guideline Committee defined the broad scope of the guideline project, which prompted the core group to invite 15 anaesthetist experts into the task force as affiliate co-authors. Georgina Imberger (Copenhagen Trial Unit and Cochrane Anaesthesia Review Group) was invited into the task force for the evidence search.

4.2 The search for evidence

To develop the scope of the guidelines, the task force defined a series of key clinical questions about the management of severe perioperative bleeding, a process completed in October 2010. These questions formed the basis for reviewing the evidence and developing the recommendations.

We used three approaches to search for relevant published evidence. First, we conducted a broad search on MEDLINE and Embase using exploded terms for 'anaesthesia' and 'surgery', combined with 'bleeding' or 'blood loss' in the title. This search was conducted in December 2010 and included all publications from the previous 10 years. The exact search strategy is detailed in the Appendix (Supplemental Digital Content, http://links.lww.com/EJA/A31). A total of 9376 citations were retrieved and reviewed for possible inclusion.

Second, we conducted more specific MEDLINE and Embase searches when necessary in some areas. Search terms were developed with the help of the task force members responsible for the given section. The exact searches are detailed in the Appendix (Supplemental Digital Content, http://links.lww.com/EJA/A31). The searches were conducted between January and May 2011, and included all publications from the previous 10 years. A total of 20 664 citations were retrieved and reviewed for possible inclusion. The search was repeated for the last sections to be included (6.3, 5.1) between May 2011 and May 2012. Third, we conducted a broad search for systematic reviews of anaesthesiological interventions. The exact search strategy is detailed in the Appendix (Supplemental Digital Content, http://links.lww.com/EJA/A31). We searched MEDLINE and Embase, with no time restrictions. A total of 11 869

citations were retrieved and reviewed for possible inclusion.

From these three approaches, a total of 2686 publications were selected for possible inclusion. We included systematic reviews, randomised controlled trials, cohort studies, case control studies and cross-sectional surveys. We did not include existing guidelines, narrative reviews, editorials, case series or case reports. We did not use language restrictions.

Task force members reviewed the selected articles relevant to their sections. Our goal was to include all relevant and robust evidence in these guidelines. Therefore, we included evidence that was sourced separately from the approaches described above and considered references cited in published trials, sometimes leading to the inclusion of trials published more than 10 years ago. Other evidence was sourced from the personal clinical and academic experience of the task force members.

The expertise of the task force guided the selection of trials for inclusion, thereby involving a subjective assessment of a study's relevance. Once selected, we reviewed trials for their quality and applicability. According to the suggestion of the ESA Guideline Committee, we used the Scottish Intercollegiate Guidelines Network (SIGN) grading system[28] to assess the level of evidence of a study and to grade our recommendations based on the body of supporting evidence. During the process of guideline development, the official position of the ESA changed, matching many other scientific organisations in favouring the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Therefore, all of our recommendations and suggestions are assigned a number (relating to the strength of the recommendation) and a letter (relating to the quality of the supporting evidence) according to the GRADE system (Table 1). Statements are accompanied only by a letter. According to the broad scope of the guideline project, the initial manuscript was approximately 98 000 words in length. In order to increase readability and future implementation, by May 2012 the contents of all sections had been condensed by approximately 46% and a list of recommendations was prepared (Section 2. Summary).

4.3 Review of the guideline

These guidelines have undergone the following review process. The final draft was reviewed by members of the relevant Subcommittees of the ESA's Scientific Committee who were not involved in the initial preparation of the guideline, as well as by external reviewers. The draft was posted on the ESA website from 13 July 2012 to 19 August 2012 and all ESA members, individual and national, were contacted by electronic mail to invite them to comment. Comments were collated by the chair of the guideline task force and the guideline was amended as appropriate. The final manuscript was approved by the Guidelines Committee and Board of the ESA before submission for publication in the European Journal of Anaesthesiology. Because of the increasing evidence in this field, an update of the guidelines is planned every two years.

5 COAGULATION MONITORING

5.1 Perioperative coagulation testing

5.1.1 Introduction

Traditionally, perioperative coagulation monitoring has relied on clinical judgement and standard laboratory tests (SLTs). However, many SLTs were designed to test for coagulation factor deficiencies, not for predicting risk of bleeding or guiding haemostatic management. Moreover, utility of SLTs in emergency situations is limited by slow turnaround times due to sample transport and plasma preparation requirements.[29–32] In contrast, viscoelastic point-of-care monitoring enables rapid intraoperative diagnosis of the cause of bleeding. This section examines assays used to diagnose coagulation status perioperatively.

5.1.2 Standard laboratory tests for coagulation monitoring

SLTs can be performed using automated analysis, with instrumentation, reagents and detection methods varying between institutions. However, the principles underlying individual SLTs are consistent across platforms.

5.1.2.1 Activated partial thromboplastin time

Activated partial thromboplastin time (aPTT) measures overall integrity of the intrinsic and common coagulation pathways. Recalcified, citrated plasma is incubated at 37°C with partial thromboplastin and an activator.[33,34] Clotting time (time to fibrin strand formation) is recorded. aPTT is affected by levels of fibrinogen and coagulation factors II, V, VIII, IX, XI, and XII, and is influenced by temperature, pH, heparin and oral anticoagulants.[35] aPTT indicates multiple coagulation factor deficiencies more clearly than it does single factor deficiencies.

5.1.2.2 Prothrombin time

Prothrombin time (PT) measures integrity of the extrinsic and common pathways; it is affected by levels of fibrinogen and coagulation factors II, V, VII and X.[35] Recalcified, citrated plasma and tissue thromboplastin are incubated at 37°C. Clotting time is recorded as for aPTT. PT measurements can be standardised by conversion to an international normalised ratio (INR) to allow monitoring of anticoagulant therapy with coumarins.

5.1.2.3 Fibrinogen concentration

Fibrinogen is essential for effective coagulation and is the first factor to be depleted during massive bleeding and haemodilution.[36] Its concentration is often determined

indirectly using the Clauss method.[37] Diluted, citrated plasma is activated with thrombin, and clotting time is recorded as for PT and aPTT. Fibrinogen concentration is inversely proportional to clotting time, and is calculated using calibration standards. Clauss assays are sensitive to heparin, fibrinogen degradation products[35] and colloids such as hydroxyethyl starch.[38–40] Fibrinogen levels can also be determined using a PT-based assay, although this may be too variable for clinical use.[41] Alternatively, immunological detection is possible using antifibrinogen antibodies, providing a measure of fibrinogen quantity but not functionality.

5.1.2.4 Platelet count

In the perioperative setting, platelet count (concentration) is commonly measured. This, however, does not assess the functional activity of platelets.

5.1.2.5 Assaying specific coagulation factors

Tests for individual coagulation factors, including factors II, V, VII, VIII, IX, X and XIII, can be used to confirm specific deficiencies (e.g. congenital). Other biomarkers of coagulation and fibrinolysis can also be measured, such as D-dimers for exclusion of pulmonary embolism and deep vein thrombosis.

5.1.3 Point-of-care coagulation monitoring

Point-of-care (POC) coagulation monitoring uses whole blood and is performed in the emergency room, operating theatre, or the central laboratory. Turnaround times for POC tests are shorter than for SLTs. As with SLTs, POC coagulation monitoring can be performed using various analytical platforms and reagents, so this section will focus on assay principles. For global coagulation analysis, the principal POC tests use thrombelastography (TEG; Haemoscope Inc., Niles, IL) or thromboelastometry (ROTEM; Tem International GmbH, Munich, Germany), which each operate on similar principles. Unless stated otherwise, the term 'POC coagulation monitoring' within this section refers to TEG/ROTEM assays.

5.1.3.1 Parameters recorded using point-of-care coagulation monitoring

Blood samples for POC coagulation analysis are placed in a reaction chamber and a pin is immersed. Oscillation is introduced and viscoelasticity of the sample is measured via movement of the pin. As the blood clots, fibrin polymerisation progressively changes the viscoelasticity. Overall, POC coagulation assays are more representative of *in vivo* coagulation than conventional laboratory tests.

Unlike SLTs, POC coagulation monitoring extends beyond initial fibrin polymerisation. The clot formation and degradation profile can be assessed for up to 60 min, with coagulation dynamics represented graphically. Numerical values indicate the speed and quality of clot formation.

Coagulation initiation. Recorded as reaction (r) time or clotting time (CT), both parameters represent the time to reach an amplitude of 2 mm (i.e. initiation of clot formation, partially dependent on thrombin generation).[42]

Clot formation. Time for amplitude to increase from 2 to 20 mm, expressed as k time or clot formation time (CFT). The alpha (α) angle (tangent of the slope between 2 and 20 mm) provides another measure of clot formation rate.

Clot strength. Maximum amplitude (MA) or maximum clot firmness (MCF), both measured in mm, represent the combined effects of platelet aggregation and fibrin polymerisation. Clot rigidity (G) and maximum clot elasticity (MCE) may also be used to assess clot strength. G and MCE have a curvilinear relationship with MA and MCF, respectively, making them conceptually and statistically important.[43,44] Amplitude at early timepoints (A5, A10, etc.) may be used to predict maximum clot firmness.

Clot stability. This is measured by reduction of clot strength after MA or MCF has been reached, and typically expressed as lysis index (LY30 or LI30; % of clot strength remaining 30 min after MA or CT, respectively). Maximum lysis (ML; greatest % decrease in amplitude [from MCF] observed during the assay period) is also used. Low lysis index or high ML can indicate hyperfibrinolysis.

5.1.3.2 Commonly used blood modification agents for POC coagulation assays

POC coagulation monitoring can be performed using recalcified, citrated blood alone (NATEM assay; clotting initiated intrinsically by the surface of the cup and pin). More usually, activators are added to accelerate coagulation, and modifying agents can suggest the cause of observed coagulopathy. The following are the most commonly used assays.

Intrinsic activation (e.g. kaoTEG or INTEM assay). Addition of a contact activator (e.g. kaolin or ellagic acid) stimulates intrinsic activation, providing an assay analogous to aPTT.

Extrinsic activation (e.g. rapidTEG or EXTEM assay). Addition of (recombinant) tissue factor (TF) activates coagulation via the extrinsic pathway, providing an assay analogous to PT.

Heparin anticoagulation (e.g. hepTEG or HEPTEM assay). Addition of heparinase to an intrinsically activated assay degrades heparin in the blood, enabling identification of coagulopathy caused by heparin.

Fibrin clot quality (e.g. functional fibrinogen [FF] or FIBTEM assay). This involves addition of a platelet inhibitor (e.g. abciximab or cytochalasin D) to an extrinsically activated assay. This test measures strength of the fibrin-based clot. Low FF/FIBTEM clot strength usually indicates fibrinogen deficiency. Adequate FF/FIBTEM

clot strength in the presence of decreased overall clot strength in bleeding patients may indicate platelet deficiency.

Hyperfibrinolysis (e.g. APTEM assay). This involves addition of the antifibrinolytic agent aprotinin to an extrinsic activation assay. Improved coagulation with aprotinin indicates hyperfibrinolysis.

POC devices with multiple channels allow several assays (e.g. extrinsic, intrinsic, fibrinogen and hyperfibrinolysis) to be performed simultaneously.

5.1.4 Which approaches can be used for preoperative evaluation of coagulation status?

Preoperative coagulation monitoring may influence subsequent decisions concerning the management of perioperative bleeding. Bleeding risk may be elevated by congenital coagulation disorders such as von Willebrand disease (VWD) or by routine medication for underlying conditions. Coagulation tests may suggest increased bleeding risk, but they cannot predict intraoperative or postoperative bleeding caused by exogenous factors. Thoracic or abdominal procedures lasting >2 h and with blood loss >500 ml carry particular risks, and may require laboratory analysis for bleeding risk stratification.[45]

5.1.4.1 Standardised bleeding history and clinical evaluation

Recommendation

We recommend the use of a structured patient interview or questionnaire before surgery or invasive procedures, which considers clinical and family bleeding history and detailed information on the patient's medication. **1C**

Structured patient interviews are a primary tool for preoperative assessment of bleeding risk. Clinical and family history and current drug therapy are considered. Recent guidelines from the UK, Austria and Italy recommend structured questionnaires.[34,45–47] Investigations have shown that such questionnaires identify patients at risk of bleeding.[48–57] In a study by Eberl *et al.*,[49] a positive predictive value of 9.2% was reported for the use of standardised bleeding history. In addition, three groups have strongly recommended a questionnaire instead of SLTs.[48,51,57] Data suggest that these questionnaires also have the potential to quantify the risk of bleeding for inherited coagulopathies.[58]

Physical examination should be performed as a second step, focusing on signs of bleeding and diseases which may cause haemostatic failure (e.g. liver disease, inherited coagulation abnormalities).[59] Physical examination can detect bleeding disorders not identified by conventional tests (e.g. scurvy presenting with soft tissue bleeding).[33] Gender, body mass index and comorbidities including arterial hypertension, diabetes mellitus and renal dysfunction are independent risk factors for bleeding and transfusion.[60–68]

Recommendation

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery. **1C**

A standardised questionnaire on bleeding and drug history is superior to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery.[52] In patients with a positive bleeding history, a physician experienced in haemostaseology or haematology should be consulted. If indicated, additional tests to assess haemostatic disorders are advisable, in particular with regard to primary haemostasis, for example, von Willebrand diagnostics, platelet function tests (PFA-100) or whole blood impedance aggregometry (Multiplate).[69,70] This concept enables goal-directed therapy of hereditary and acquired disorders of primary haemostasis.[52,70–72] However, the value of PFA-100 in detecting preoperative disorders of primary haemostasis is still under discussion.[73,74] Although, an increasing number of patients are treated with dual antiplatelet therapy guided by PFA-100, the primary ADP-cartridge is not able to detect the effect of ADP-receptor antagonists, such as thienopyridines, reliably.[74–77] In addition, the new Innovance® PFA P2Y cartridge is yet to be evaluated for this purpose.[78,79]

5.1.4.2 Preoperative use of standard laboratory tests

Application of preoperative SLTs is well covered by existing guidelines.[34,46,80] However, current ESA guidelines do not recommend their use.[81] SLTs were originally designed to indicate coagulation factor deficiencies, not to assess clinical risk of haemorrhage.[82,83] Normal ranges for PT and aPTT are based on the general population and may not apply to surgical patients with massive bleeding.[82] Accordingly, aPTT and PT fail to identify occult bleeding disorders among paediatric patients at high risk of bleeding.[84]

Low preoperative fibrinogen concentrations potentially indicate increased risk of intraoperative bleeding during cardiac surgery.[85,86] In the obstetric setting, fibrinogen measurement is reported as the parameter best correlated with postpartum bleeding volume and haemostatic impairment.[87] Preoperative measurement of fibrin monomer or fibrin degradation product may also allow risk stratification for intraoperative blood loss.[88,89]

SLTs are typically performed using plasma, with platelets and other blood cells removed, and thus do not reflect the true physiological clotting process.[90] Nor can SLTs provide rapid assessment of fibrinolysis, platelet dysfunction, or haemostatic response to injury or surgery. A systematic review found that abnormal SLT results do not predict intra- or postoperative bleeding.[91] False positive and false negative results are likely,[92] necessitating further tests and incurring additional costs. Italian

guidelines recommend routine preoperative PT, aPTT and platelet count assessment.[46] However, in patients without a previous history of bleeding or bleeding disorders, SLTs are not generally recommended.[33,34,47,59,80,82,93–95] Selective laboratory testing is advised because it is more cost-effective and more evidence based.[92,95] Preoperative assessment of aPTT, PT, INR, fibrinogen and platelet count is warranted in patients with bleeding disorders, a history of bleeding or a clear clinical indication (e.g. HELLP syndrome [haemolysis, elevated liver enzymes and low platelets], liver disease, leukaemia or haemophilia).[34,46] There is currently little evidence to support additional, routine application of point-of-care INR testing in the preoperative setting to predict bleeding tendency, despite the fact that many recent devices provide results which are comparable with laboratory testing.

5.1.4.3 Preoperative use of POC coagulation monitoring

Preoperative POC measurement of coagulation does not predict bleeding during or after surgery.[96–100] POC monitoring assays are instead designed for rapid diagnosis of bleeding causes, which is of most value intraoperatively. Indiscriminate preoperative coagulation monitoring using POC assays is unlikely to be cost-effective, but it may be warranted in combination with SLTs in patients with bleeding disorders such as VWD, factor XII deficiency, and haemophilia A with dysfibrinogenaemia.[101]

5.1.4.4 What is the role of genetic predictors?

In neurosurgery patients, tumour necrosis factor-alpha polymorphism is associated with increased bleeding risk.[102,103] Low levels of plasminogen activator inhibitor-1 (PAI-1) correlate with increased bleeding risk in transurethral resection of the prostate;[104] PAI-1 polymorphism may also influence bleeding risk in cardiac surgery.[105] Polymorphism of GPIIIa can exacerbate bleeding in cardiac surgery following aspirin pretreatment.[106] Angiotensin converting enzyme II genotype may be associated with reduced blood loss in geriatric patients undergoing hip arthroplasty.[107] In addition, polymorphisms have been identified in seven distinct factors which may contribute to the wide variation in bleeding tendency.[108] E-selectin polymorphism has also been identified as a risk factor for increased bleeding during cardiopulmonary bypass (CPB).[109]

Currently, no recommendation can be made on the value of genetic testing for evaluating bleeding risk.

5.1.4.5 What is the best approach for preoperative evaluation of coagulation status?

Assessment of bleeding history, including physical examination, remains the best tool for identifying patients with increased risk of perioperative bleeding complications. If bleeding history is positive, clinical signs of bleeding tendency are present, or if the planned operation requires special consideration, comprehensive assessment is indicated. Otherwise, the only crucial blood analysis is ABO blood grouping.[110]

5.1.5 Which coagulation monitoring tests can be used to guide intraoperative haemostatic therapy?

Correct diagnosis of the cause of bleeding is essential for effective haemostatic intervention. In emergency situations and high-risk surgical procedures, this diagnosis must be made as quickly as possible. Intervention can be guided by clinical judgement, SLTs or POC monitoring. We discuss the evidence for each below.

5.1.5.1 Intraoperative use of standard laboratory tests

Several guidelines have explored intraoperative use of SLTs.[46,110–112] There is little evidence to support their utility in this setting. Measurement of fibrinogen (Clauss method), D-dimer and antithrombin (AT) may, in conjunction with clinical assessment and SLTs, facilitate diagnosis or exclusion of disseminated intravascular coagulation (DIC).[112] This approach, however, is incompatible with emergency situations because SLTs have typical turnaround times of 30–60 min.[35,113] Accordingly, the applicability of SLTs in trauma has never been proven.[113] In cardiovascular surgery, hypofibrinogenaemia has been identified as a major factor contributing to haemorrhage after CPB;[114] however, for laboratory measurement of fibrinogen to be useful, analysis would need to begin before the patient is removed from CPB, which is prevented by sensitivity of the Clauss assay to heparin. In liver transplantation, attempts to establish transfusion triggers for haemostasis management, based either on SLTs or POC monitoring assays, have been inconclusive.[115]

There is insufficient data to recommend routine intraoperative coagulation monitoring using SLTs.[95] Conversely, recent Italian guidelines recommend prolonged PT and aPTT (>1.5 times normal) as a trigger for administration of fresh frozen plasma (FFP);[112] the same guidelines also suggest 'blind' FFP administration if the tests cannot be performed within a reasonable time. A recent review of haemostatic test results during postpartum haemorrhage found that FFP was routinely over administered with respect to guidelines for PT- and aPTT-guided transfusion.[87] Moreover, fibrinogen concentrations declined in many patients despite excessive FFP transfusion, suggesting that alternative interventions may have been more suitable.

5.1.5.2 Intraoperative use of point-of-care coagulation monitoring

A recent Cochrane review showed a lack of evidence that POC monitoring improves mortality compared with 'usual care'.[17] This is unsurprising given that POC monitoring assays only establish the presence and cause

of haemostatic impairment; it is the subsequent interventions that influence patient outcome. Bleeding may be reduced by improving consistency of therapeutic decisions, using different transfusion triggers or using alternative interventions. For example, POC monitoring is used to guide administration of coagulation factor concentrates, which has been shown to decrease allogeneic blood product transfusion requirements and was associated with improved outcomes.[116–120] The techniques (e.g. thrombelastography) and devices (e.g. TEG) are routinely given prominence over the individual assays. Some studies have used a single assay (e.g. kaolin activation)[121,122] but simultaneous performance of several assays may be critical for accurate diagnosis of bleeding causes. Selection of appropriate assays for POC diagnosis should be considered carefully.[123]

Intraoperative point-of-care monitoring in trauma. POC coagulation monitoring has been used in case studies and patient cohorts to diagnose and treat bleeding in trauma patients.[118,124–126] CT and MCF from extrinsic activation (TF) and fibrin clot quality (TF + cytochalasin D) assays,[118,124,125] as well as CT, CFT and MCF from intrinsic activation (ellagic acid) assays,[126] have been used successfully to monitor haemostasis and guide treatment with fibrinogen concentrate and prothrombin complex concentrate (PCC). Such treatment has been shown to reduce exposure to allogeneic blood products compared with non-standardised strategies which do not utilise POC coagulation monitoring.[118] The evidence suggests that POC assays measuring extrinsic activation and fibrin clot quality may be useful to guide administration of fibrinogen concentrate and PCC in trauma. Prospective, randomised trials are now required.

Additional case studies describe POC coagulation monitoring in trauma patients. Nylund *et al.*[127] reported rFVIIa administration in a paediatric trauma patient in response to poor k and α-angle values obtained by intrinsic (kaolin) activation assay. Walker *et al.*[128] reported the assessment of MCF in extrinsic (TF) and fibrin clot quality (TF + cytochalasin D) assays before epidural insertion after massive transfusion.

Intraoperative point-of-care monitoring in cardiovascular surgery. The value of POC monitoring to guide haemostatic therapy following CPB has been demonstrated in several randomised, controlled trials.[119,121,129] In one of them, four parallel assays (intrinsic [ellagic acid], intrinsic + heparinase, extrinsic [TF] + aprotinin, and extrinsic + cytochalasin D) were used to guide haemostatic intervention in patients undergoing aortic surgery with circulatory arrest.[129] Furthermore, first-line therapy with fibrinogen concentrate and PCC based on POC testing was associated with decreased transfusion requirements and a decreased incidence of thromboembolic events in a cohort study including 3865 patients[120] as well as in a prospective randomised controlled trial including 100 patients.[119] In this latter study, the use of an algorithm based on POC testing was associated with improved outcomes including significantly reduced mortality. Routine use of such algorithms could reduce transfusion requirements, improve outcomes and lower costs.

Prospective studies have also demonstrated the utility of MCF from fibrin clot quality assessment (TF + cytochalasin D) to guide administration of fibrinogen concentrate in cardiovascular surgery patients (target MCF: 22 mm).[116,117] These studies suggest that individualised fibrinogen concentrate dosing, based on target MCF values, may decrease blood loss and transfusion requirements following CPB.

Similar individualised dosing of cryoprecipitate, based on A10 values from fibrin clot quality assays (TF + cytochalasin D), has been reported following elective CPB.[131] Prediction of cryoprecipitate requirements using this approach has high sensitivity and specificity.

Intraoperative point-of-care monitoring in liver surgery. Individualised ('theragnostic') dosing of cryoprecipitate using thrombelastography has been described in a liver transplant patient with afibrinogenaemia.[132] More recently, a transfusion algorithm based on POC intrinsic (kaolin) activation test results was compared with an SLT based protocol in orthotopic liver transplantation (OLT) patients.[133] Mortality was unaffected and the authors reported reduced exposure to FFP using the POC guided algorithm. Overall, the results indicate that POC intrinsic activation assays can be used to guide transfusion during OLT surgery.

A retrospective study investigated routine POC monitoring of fibrinolysis in OLT, using extrinsic (TF) activation and hyperfibrinolysis (TF + aprotinin) tests to determine whether tranexamic acid should be administered.[134] This targeted approach to antifibrinolytic therapy may improve patient responses and reduce exposure to FFP.

Intraoperative point-of-care monitoring in obstetrics. POC assays with intrinsic (ellagic acid) and extrinsic (TF) activation, as well as fibrin clot quality (TF + cytochalasin D), have been compared in pregnant women and non-pregnant controls.[135] Clotting time and clot formation time were reduced and clot strength was increased in the pregnant group, demonstrating hypercoagulability. Studies are needed to ascertain the potential use of POC monitoring for treating postpartum bleeding, and to determine an appropriate range of reference values for these patients.

Additional POC techniques have been described, for example, POC assessment of PT and INR, which appears to be rapid and accurate.[136] However, the usefulness of PT/INR may be limited outside the setting of vitamin K antagonist anticoagulation.

5.1.6 Postoperative evaluation of coagulation status

Potential complications following surgery include thromboembolic events and, conversely, recurrent or excessive bleeding. Postoperative coagulation monitoring in the intensive care unit (ICU) can provide information regarding appropriate haemostatic interventions or further procedures which may be required.

Kashuk *et al.*[137] assessed the use of POC extrinsic (TF) activation tests to identify critically ill patients at risk of thromboembolic events. Hypercoagulability, defined as G $>12\,400\,\mathrm{dyn\,cm^{-2}}$, was confirmed in 86/152 patients. Clot strength (MA from POC assays) has been used to measure the effects of clopidogrel after coronary artery bypass surgery.[138] In splenectomised thalassaemic patients, whole blood intrinsic (ellagic acid) and extrinsic (TF) activation assays consistently indicated hypercoagulability, while thrombin generation tests performed using platelet-poor plasma did not.[139] Other evidence from POC assays, aPTT, platelet counts and fibrinogen measurement has confirmed a tendency towards hypercoagulability following splenectomy.[140] Current evidence suggests that POC measurements of the speed of clot initiation, formation and strength/elasticity/rigidity, can identify patients at risk of thromboembolic events.

There is minimal evidence to support using either SLTs or POC coagulation monitoring to guide haemostatic intervention in the postoperative period. Trials comparing POC guided transfusion with conventional coagulation management have included analysis of samples drawn up to 24 h after CPB, but have not reached specific conclusions on the importance of postoperative monitoring.[121,129]

5.1.7 Are patient outcomes improved by algorithms that incorporate coagulation monitoring for perioperative haemostatic management?

Recommendations

We recommend the application of transfusion algorithms incorporating predefined intervention triggers to guide haemostatic intervention during intraoperative bleeding. **1B**

We recommend the application of transfusion algorithms incorporating predefined intervention triggers based on POC coagulation monitoring assays to guide haemostatic intervention during cardiovascular surgery. **1C**

Haemostatic intervention in bleeding patients is generally determined empirically. Consequently, transfusion practices differ substantially among institutions.[141–143] To reduce this variability, guidelines typically recommend administration of blood products according to predefined transfusion triggers which can be measured using coagulation tests. In a review of trigger guided transfusion during cardiovascular surgery, use of an algorithm significantly reduced patient exposure to allogeneic blood products in seven out of eight studies.[144]

Long turnaround times may preclude the use of some tests in emergency situations. Even in the absence of definitive evidence, implementation of POC assays appears rational if the alternative is haemostatic management guided by clinical judgement alone.[119,120] A prospective study recently demonstrated superior turnaround times, and quality of assessment, with POC monitoring compared with PT and aPTT.[31] Transfusion algorithms incorporating POC coagulation monitoring are effective in reducing blood loss, reducing exposure to allogeneic blood products and improving the safety and cost-effectiveness of haemostatic therapy in cardiac surgery.[121,129,144]

Perioperative coagulation monitoring is beneficial only if the results contribute to clinically effective decisions. Patients with similar conditions may receive different treatments if protocols and triggers for coagulation management are not in place.[145] In a study of transfusion triggers used for bleeding management in OLT patients, substantial variability was observed in transfused quantities of FFP, platelets and cryoprecipitate when different monitoring assays were used.[115] The authors concluded that further studies would be required to determine optimal monitoring procedures for guiding haemostatic intervention.

5.2 Evaluation of platelet function

Identification of platelet function is important for informing perioperative haemostatic management. There are several methods for assessing platelet function, each with its own limitations. The number of existing devices and their clinical validation is constantly evolving as is their utility in various settings. In this section, we will briefly address some of the existing commercial tests with sufficient clinical validation. However, separation of these devices into different subsets of sections does not exclude their application in other clinical settings.

Recommendations

We suggest preoperative platelet function testing only in addition to a positive bleeding anamnesis. **2C**

We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions and antiplatelet medication. **2C**

5.2.1 Which platelet function tests can be used preoperatively for identifying disturbances of primary haemostasis?

The Platelet Function Analyser (PFA-100®, Siemens, Tarrytown, NY) test can be performed at the point-of-care to rapidly identify platelet defects before surgery.[52,146] It has shown high sensitivity and specificity

for platelet function screening performed preoperatively in patients with a positive bleeding history.[52]

The PFA-100 test measures platelet response to agonists in citrated whole blood and can be used preoperatively at the point-of-care. However, the PFA-100 has demonstrated a relatively low predictive value for bleeding risk.[146] In cardiac surgery patients, preoperative PFA-100 data have been shown to correlate with postoperative blood loss in some studies[147] but not others.[148]

The Cone and Plate(let) Analyser (CPA, Impact-R) test has been used successfully for screening of primary haemostasis abnormalities such as von Willebrand disease.[149–151] The test can detect disturbances in primary haemostasis by measuring deposition of platelets from whole blood on to an artificial surface.

5.2.2 Preoperative platelet function testing in different clinical settings

5.2.2.1 Trauma

In a study of trauma patients, platelet function measured using the PFA-100 analyser showed a significant difference between survivors and non-survivors.[152] To be useful in an emergency, a platelet function test needs to be applicable at the point-of-care and be capable of generating results quickly. A recent study used multiple electrode aggregometry (MEA, Multiplate) to assess platelet function of trauma patients on admission to the emergency room.[153] ADPtest and TRAPtest values below the normal range were associated with increased mortality.[153]

5.2.2.2 Cardiac surgery

The MEA ADPtest has provided results comparable with light transmittance aggregometry (LTA; considered as the 'gold standard' in platelet function testing) in coronary artery bypass graft (CABG) patients not taking antiplatelet therapies.[154] Platelet dysfunction is a major cause of bleeding following cardiac surgery.[155,156] Platelet activation (dysfunction) has been shown using HemoSTATUS® (Medtronic, Minneapolis, MN) testing during CPB.[157]

MEA measurements taken preoperatively correlate closely with subsequent platelet transfusion requirements, more so than Impact-R tests.[158] When selecting a platelet test for use during cardiac surgery, awareness of antiplatelet therapy is crucial because this may exacerbate surgical bleeding.[47] As well as correlating with platelet transfusion requirements,[158] the MEA ADPtest (performed 0.5–1 days before surgery) can predict postoperative bleeding in patients taking thienopyridines and undergoing CPB.[159]

Three recently published studies (one retrospective and two prospective randomised clinical trials) have shown that perioperative platelet function testing using MEA or TEG Platelet Mapping in combination with ROTEM or TEG analysis is associated with reduced bleeding, reduced transfusion requirements, reduced costs and improved outcomes in cardiac surgery.[119,120,160]

5.2.2.3 Liver surgery

Flow cytometry has been used to quantify platelet activation during liver transplantation, from the preoperative through to the postoperative period.[161] Whole blood impedance platelet aggregometry has been used to correlate platelet activation with ischaemia/reperfusion injury in paediatric liver transplantation.[162]

Patients with liver disease may display altered platelet count[163,164] and platelet function.[165–167] In this setting, there is little evidence to indicate whether current diagnostic tests are useful for the preoperative identification of patients with increased perioperative bleeding risk.[168] Flow cytometry provides no evidence of systemic platelet activation during liver transplantation.[161]

5.2.2.4 Obstetrics

Among pregnant women with type 1 Gaucher disease, abnormal CPA results have been associated with increased risk of peripartum haemorrhage.[169] Furthermore, a study using a modified LTA assay found that patients with unexplained recurrent miscarriage have significantly increased platelet aggregation in response to arachidonic acid, providing a rationale for using aspirin in this setting.[170]

5.2.3 Which platelet function tests can be used preoperatively for identifying the effects of antiplatelet therapy?

Before surgery the medical history should be taken and the patient's exposure to antiplatelet medication should be determined.[47,171] In patients with a positive bleeding anamnesis, full blood count, including examination of platelet count and size,[172] and PFA-100 collagen-epinephrine and collagen-ADP[52] are first level tests in preoperative evaluation. Antiplatelet therapy is associated with increased risk of perioperative bleeding but there is no consensus on the optimal timing of preoperative discontinuation. Reduced platelet function caused by antiplatelet medication can be quantified by evaluating the response to platelet agonists preoperatively.

Depending on the test reagent used, MEA is sensitive to aspirin, thienopyridines and glycoprotein (GP) IIb/IIIa inhibitors (e.g. abciximab), and has been used successfully for differential diagnosis.[173–175] MEA provides differential diagnostic information by using platelet agonists as test reagents (e.g. collagen, arachidonic acid, ADP, thrombin receptor activator peptide [TRAP], von Willebrand factor [VWF]).[173–175] However, clinical trials are needed to assess the value of MEA in perioperative monitoring of aspirin and clopidogrel.

PlateletWorks (Helena Laboratories, Beaumont, TX) is an electronic impedance based cell counting method, allowing point-of-care measurement of platelet count and aggregation. PlateletWorks has the potential for monitoring clopidogrel reversal[176] and is sensitive to the effects of aspirin and GPIIb/IIIa inhibitors (e.g. abciximab).[177,178]

VerifyNow is a point-of-care turbidimetric test which detects agonist-induced platelet aggregation in whole blood samples. It can monitor the effects of aspirin, thienopyridines and GPIIb/IIIa inhibitors. The VerifyNow $P2Y_{12}$ assay performed before heparinisation (prior to coronary stenting) has successfully identified patients on clopidogrel and at risk of atherothrombotic complications but did not identify those at risk of bleeding.[179]

The PFA-100 test can be used to monitor the effects of desmopressin or antiplatelet therapy with aspirin but not with thienopyridines.[180]

5.2.4 Which platelet function tests can be used intraoperatively for monitoring the effects of surgery?

Platelet function decreases intraoperatively, irrespective of surgery type. Static tests which capture only a single time point do not reflect the dynamic nature of coagulopathic bleeding. For example, LTA is not suitable for intraoperative platelet function testing because of the long turnaround time. Point-of-care tests which can be performed rapidly are required, e.g. the HemoSTATUS platelet function test, MEA and PlateletWorks (clinical data are lacking for PlateletWorks). In general, a platelet count of $\geq 100\ 000\ \mu l^{-1}$ is needed for quantitative analysis.

5.2.4.1 Blood loss and synthetic colloid or crystalloid replacement

Platelet count decreases intraoperatively through major blood loss and dilution from volume resuscitation. Synthetic colloids or crystalloids may affect platelet function,[181] although it has also been reported that these agents have no effect.[182] Further studies are required to ascertain the effects of synthetic colloids and the most appropriate point-of-care tests to evaluate these effects.

5.2.4.2 Monitoring therapeutic interventions

Both PFA-100 and MEA have been used successfully to assess improvement in platelet function intraoperatively following administration of desmopressin.[71,93,183] Platelet transfusion therapy can be guided and monitored using point-of-care testing, for example with the PFA-100 collagen and epinephrine (CEPI), and collagen and ADP (CADP) assays.[184] Following platelet transfusion, PFA-100 results provided a better indication of transfusion outcome than the previous 'gold standard', the corrected count increment (CCI).[184]

5.2.4.3 Point-of-care testing immediately after surgery and on arrival at the intensive care unit

Following discontinuation of CPB, patients with severe aortic stenosis[183] or drug- or CPB-induced platelet dysfunction[119] may benefit from desmopressin. These patients can be identified using HemoSTATUS, a point-of-care test which measures platelet function independently of platelet count.[185] Upon arrival at the ICU, patients at risk of requiring platelet transfusion have been identified using MEA.[186]

5.2.4.4 Which platelet function tests can be used postoperatively for monitoring haemostasis?

MEA has been used successfully to detect changes in platelet function after cardiac surgery.[154,187] Platelet function testing (e.g. PFA-100) can be used to detect changes in platelet reactivity after surgery and to monitor the effectiveness of antiplatelet medication. However, evidence for the postoperative use of platelet function tests is limited.

5.2.4.5 Are patient outcomes improved by algorithms which incorporate platelet function testing for intraoperative haemostatic monitoring?

Both laboratory and point-of-care platelet function tests are included in some algorithms for managing perioperative bleeding[188,189] but there is currently insufficient evidence to answer this question definitively.

6 ANAEMIA MANAGEMENT

6.1 Preoperative correction of anaemia

6.1.1 Introduction

Perioperative anaemia increases the risk of numerous complications such as cardiac events, pneumonia and postoperative delirium.[190,191] Associations between anaemia and higher rates of both morbidity and mortality are well established for patients undergoing cardiac surgery.[192,193] A recent, large cohort study demonstrated that these associations also apply to non-cardiac surgery; the odds ratio for mortality among patients with anaemia versus those without was 1.42.[194] Preoperative anaemia has been shown to be predictive for perioperative transfusion of allogeneic blood products such as red blood cells, which itself carries a significant risk of adverse events and mortality.[192,195,196] There is some tolerance to postoperative anaemia among patients without cardiovascular disease, but for each $1\ g\ dl^{-1}$ decrease in postoperative haemoglobin concentration below $7\ g\ dl^{-1}$, mortality has been shown to increase by a factor of 1.5.[191] Estimates of the prevalence of anaemia in surgical patients range widely, from 5% to 76%.[197] High rates have been reported in cancer patients (e.g. breast cancer, colon cancer), while lower rates have been observed in orthopaedic patients.[197,198]

Allogeneic blood transfusion has long been used for correcting perioperative anaemia. However, there is a

general move to minimise this approach due to shortcomings associated with allogeneic blood products, such as limited blood supply and safety concerns.[190] Among patients undergoing transurethral resection of the prostate, a low preoperative haemoglobin concentration has been reported as the only reversible factor with the potential to reduce transfusion.[199] Preoperative autologous blood donation has been suggested as one means of treating perioperative anaemia while avoiding transfusion of allogeneic blood products. However, the process of donation increases the risk of preoperative anaemia and it is contraindicated in patients with pre-existing anaemia.[198,200] Alternative means of managing perioperative anaemia include iron supplementation and administration of erythropoietin-stimulating agents, as well as cell salvage and restriction of postoperative blood withdrawal.[190]

6.1.2 Preoperative assessment

Recommendation

We recommend that patients at risk of bleeding are assessed for anaemia 4–8 weeks before surgery. **1C**

This recommendation is essentially empirical. There are no trials proving whether assessment of patients has an impact on their outcomes, or proving the optimum time before surgery when patients should be assessed. However, as interventions have been shown to be effective among patients with anaemia, it is valuable to assess patients before elective surgery to allow the possibility of treating anaemia before the procedure, and the period of 4–8 weeks provides enough time for treatment to take effect.

Recommendation

If anaemia is present, we recommend identifying the cause (e.g. iron deficiency, renal deficiency or inflammation). **1C**

This is another empirical recommendation. There are numerous possible causes of anaemia, and accurate diagnosis enables appropriate treatment to be administered before surgery. There are no clinical trials comparing outcomes among patients with or without accurate diagnosis of their anaemia.

Accurate diagnosis requires a work-up after determination of a low haemoglobin concentration.[191,201,202] Serum ferritin concentration below $30\,\mu g\,l^{-1}$ signifies nutritional iron deficiency for which iron therapy is administered, although referral to a gastroenterologist may be considered to rule out malignancy.[191] A serum ferritin concentration of $30–100\,\mu g\,l^{-1}$ signifies possible iron deficiency, while a concentration above $100\,\mu g\,l^{-1}$ indicates that anaemia is related to causes such as chronic disease (renal or otherwise) or inflammation. In this case, further tests are needed (e.g. assessment of renal function and vitamin B_{12}/folic acid concentrations) to ascertain the diagnosis.[191,201,202]

6.1.3 Preoperative treatment

Recommendation

We recommend treating iron deficiency with iron supplementation (oral or intravenous). **1B**

Most (though not all) studies report that preoperative oral iron supplementation is effective in raising haemoglobin concentration and decreasing perioperative transfusion. Two controlled studies have investigated the effects of at least 2 weeks of preoperative oral iron supplementation. The first was a retrospective comparison of colorectal surgery patients with anaemia who either received or did not receive iron supplementation.[203] The second was a randomised, placebo-controlled trial of oral ferrous sulphate, also performed in the colorectal surgery setting, with patients recruited whether or not they had anaemia.[204] In both of these studies, iron supplementation produced a significant increase in haemoglobin concentration, as well as significantly decreased blood transfusion rates during surgery.

The efficacy of oral iron has also been demonstrated in patients with anaemia. In a study by Cuenca *et al.*,[205] oral iron supplementation was taken for 30–45 days preoperatively by knee replacement surgery patients. Reduced transfusion of allogeneic blood products was observed, compared with a retrospective control group not receiving iron. This was the case for patients with anaemia (haemoglobin [Hb] $<13.0\,g\,dl^{-1}$) as well as those with higher haemoglobin concentrations. In another study, a significant $1.1\,g\,dl^{-1}$ increase in haemoglobin concentration was observed in response to 4 weeks preoperative treatment with oral iron supplementation among hip or knee replacement patients with anaemia (Hb $<12.0\,g\,dl^{-1}$ before iron supplementation).[206] Furthermore, Quinn *et al.*[207] showed in a prospective observational study that oral iron sulphate (200 mg, three times daily for a median of 39 days) increased haemoglobin concentration by $1.73\,g\,dl^{-1}$ ($P < 0.001$) among colorectal cancer surgery patients presenting with preoperative anaemia.

In contrast to the results described above, one prospective, observational study reported that oral iron supplementation is not effective for increasing haemoglobin concentration.[208] Eighty seven patients with haemoglobin concentrations between 10.0 and $15.0\,g\,dl^{-1}$ received iron sulphate (300 mg three times daily) for at least 3 weeks before hip or knee arthroplasty, and a $0.14\,g\,dl^{-1}$ decrease in haemoglobin concentration ($P = 0.015$) was observed.

Although oral iron supplementation may be suitable for a high proportion of patients, there are some in whom intravenous iron should be considered, e.g. for patients unable to tolerate oral iron (usually due to gastrointestinal side effects).[190]

Among women with complicated pregnancy or complicated childbirth, intravenous iron sucrose has been shown

to increase haemoglobin concentration by 2.1 g dl^{-1} within 7 days of administration.[209] A comparator group of patients received oral iron supplementation, and these women showed no increase in haemoglobin concentration (possibly because of the short time period). In another study of intravenous iron sucrose, administered preoperatively to patients scheduled for orthopaedic surgery, a significant increase in haemoglobin concentration was observed.[210] Munoz *et al.*[211] reported in a prospective, observational study that intravenous iron sucrose (mean dose 1000 mg), administered over 3–5 weeks to patients with preoperative anaemia, increased haemoglobin concentration by 2.0 g dl^{-1} ($P < 0.001$), resolving anaemia in 58% of patients.

In contrast to these results, a randomised controlled trial performed in 60 patients undergoing colorectal cancer resection reported that intravenous iron administered 14 days before surgery had no impact on haemoglobin concentration, in comparison with placebo.[212]

Intravenous iron may provide a greater increase in haemoglobin concentration than oral iron. In a randomised, prospective study, women with anaemia caused by menorrhagia (Hb < 9.0 g dl^{-1}) were treated with intravenous iron sucrose (total calculated iron deficit divided into two ampoules, three times per week) or oral iron protein succinylate daily.[213] Treatment was administered during the 3 weeks before elective surgery, and a significantly greater increase in haemoglobin concentration was observed in the intravenous group (3.0 vs. 0.8 g dl^{-1}, $P < 0.0001$).

One study has shown that preoperative intravenous iron can reduce transfusion among patients undergoing surgery for trochanteric hip fracture.[214] The transfusion rate was 39.1% among patients receiving intravenous iron, compared with 56.7% in a retrospective control group. In contrast, a randomised controlled trial performed in patients undergoing colorectal cancer resection showed that transfusion rates were no different between patients receiving preoperative intravenous iron or placebo.[212]

Intravenous iron appears to be well tolerated. Older preparations of iron for intravenous administration were associated with a risk of anaphylactic reactions.[190] However, a number of studies performed in recent years have reported a lack of adverse events associated with intravenous iron,[209,210,214,215] while others have reported favourable tolerability.[213] Today's intravenous iron preparations may therefore be considered as being much safer than those available in previous decades, although the possibility of adverse events such as hypotension, arthralgia, abdominal discomfort and back pain remains.[190] Other safety concerns with intravenous iron include infection and cancer progression,[190] but prospective data confirm lack of association with bacteraemia[216] and there are no data to confirm increased risk of cancer progression.

Recommendation

If iron deficiency has been ruled out, we suggest treating anaemic patients with erythropoietin-stimulating agents. **2A**

Erythropoietin reduces transfusion of allogeneic blood products, although not in patients with near normal haemoglobin concentrations and not in patients undergoing colorectal cancer surgery. In a meta-analysis of cardiac surgery and orthopaedic surgery studies, reduced perioperative transfusion of allogeneic blood products was observed among patients receiving erythropoietin.[217] The odds ratio for the proportion of patients transfused with allogeneic blood with erythropoietin was 0.36 ($P = 0.0001$) in orthopaedic surgery and 0.25 (not significant) in cardiac surgery. The dose of erythropoietin had no statistically significant effect on the odds ratio. Another meta-analysis examined the effect of erythropoietin on allogeneic blood transfusion among patients undergoing cardiac surgery.[218] For patients not undergoing autologous blood transfusion, the relative risk of allogeneic blood transfusion with erythropoietin was 0.53 ($P < 0.01$), and for those undergoing autologous blood transfusion, the relative risk was 0.28 ($P < 0.001$). In contrast to these meta-analyses, a Cochrane review of pre- and perioperative erythropoietin among colorectal cancer surgery patients reported no significant effect on the proportion of patients receiving allogeneic blood transfusion.[219] A meta-analysis of studies of erythropoietin-stimulating agents in a broader population of cancer patients showed that these agents can reduce the need for red blood cell transfusions with no impairment of survival.[220] However, in this context, erythropoietin-stimulating agents are recommended only according to the label (i.e. start treatment only if haemoglobin concentration is <11.0 g dl^{-1}, and discontinue treatment when the haemoglobin concentration increases to 12.0–13.0 g dl^{-1}), because when used off-label (i.e. to achieve higher concentrations of haemoglobin), they are associated with reduced survival among cancer patients.[220]

Individual randomised controlled trials have reported significant reductions in allogeneic blood product transfusions among patients undergoing orthopaedic surgery,[221–225] cardiac surgery[226] and surgery for colorectal cancer[227–229] or other gastrointestinal tract malignancies.[230] However, the effect of erythropoietin on transfusion rates has been shown to be non-significant in hip replacement patients with near normal preoperative haemoglobin concentrations,[231] radical prostatectomy patients with near normal haematocrit[232] and colorectal cancer patients with anaemia.[233]

Based on the available data, erythropoietin-stimulating agents have been recommended for orthopaedic surgery patients with anaemia, in whom nutritional deficiencies are absent or have been corrected.[191]

Two large, randomised controlled trials have shown the potential for erythropoietin to increase haemoglobin concentration. The first, involving 695 orthopaedic surgery patients with preoperative haemoglobin concentrations between 10.0 and 13.0 g dl^{-1}, showed that preoperative epoietin alpha produced higher haemoglobin concentrations from the day of surgery until discharge from hospital ($P < 0.001$).[224] In the second study, involving 204 colorectal cancer surgery patients, those receiving preoperative epoietin alpha 300 IU kg^{-1} per day showed significantly higher haemoglobin concentrations than controls on the day before and the day after surgery.[227] Significant increases in haemoglobin concentrations have been reported in several other randomised controlled trials of preoperative erythropoietin performed in patients undergoing orthopaedic surgery,[234] gynaecological cancer surgery[235] and hysterectomy.[236,237]

Treatment with epoietin alpha (40,000 IU on preoperative days 21, 14, 7 and 1) was shown in a prospective, observational study to increase haemoglobin concentrations in orthopaedic surgery patients by 2.0 g dl^{-1} and 1.8 g dl^{-1} in patients aged $\geq$65 years and <65 years, respectively.[238] In a second study of orthopaedic surgery patients performed by the same group, a similar increase in haemoglobin concentration was observed in response to similar preoperative treatment with epoietin alpha.[239] Another prospective, non-randomised study of preoperative recombinant human erythropoietin reported dose-dependent increases in haemoglobin concentrations among gynaecological surgery patients both before surgery and on discharge.[240] In an earlier study, epoietin alpha at a dose of 600 IU kg^{-1} weekly provided a larger increase from baseline in haemoglobin concentration compared with a daily dose of 300 IU kg^{-1}.[241]

There may be a risk of thrombotic complications with erythropoietin-stimulating agents, and prophylaxis for deep vein thrombosis (DVT) should be considered. Early studies did not show an increased risk of DVT among patients receiving erythropoietin.[190,242] A meta-analysis published in 1998 reported a lack of 'convincing evidence' that erythropoietin causes thrombotic complications,[217] although an increased occurrence of such events was noted in some studies with limited patient numbers. More recent studies of erythropoietin (or epoietin alpha), designed primarily to assess efficacy, have suggested a lack of significant safety concerns.[224,240,243] In addition, a Cochrane review of erythropoietin in colorectal cancer surgery reported no significant difference in thrombotic events between patients receiving erythropoietin and controls.[219]

However, data from an open-label study involving 681 spinal surgery patients showed a clear increase in the incidence of DVT among recipients of erythropoietin.[190] Similarly, in a randomised, open-label study of epoietin alpha versus standard care involving 680 spinal surgery patients, DVT, diagnosed either by Doppler imaging or by adverse event reporting, occurred in a higher proportion of patients in the epoietin alpha group.[242] Such data prompted the Food and Drug Administration (FDA) to require a warning to be added to the package inserts for erythropoietin and darbepoietin alpha, stating that DVT prophylaxis should be considered.

Recommendation

If autologous blood donation is performed, we suggest treatment with erythropoietin-stimulating agents in order to avoid preoperative anaemia and increased overall transfusion rates. **2B**

A meta-analysis has shown that autologous blood donation reduces transfusion of allogeneic blood products, but that it increases overall transfusion rates. Other studies suggest that autologous blood donation does not necessarily reduce allogeneic blood transfusion. In a large retrospective study involving 541 spinal surgery patients, those undertaking autologous blood donation had 1/25 of the chance of requiring allogeneic blood products compared with control patients who did not donate.[244] However, the overall transfusion rate was higher in the autologous donation group. These results reflect those of a Cochrane meta-analysis which concluded that, although autologous blood transfusion reduces allogeneic blood transfusion, overall transfusion (including autologous blood) is increased.[245] A randomised controlled trial performed in 32 cardiac surgery patients reported that autologous blood donation was associated with decreased allogeneic blood transfusion (0.59 vs. 5.01 U per patient).[246] However, this result may have been influenced by the fact that blood donation patients also received 3 weeks of treatment with recombinant human erythropoietin.

Evidence from other studies suggests that autologous blood donation may not reduce patients' exposure to allogeneic blood products. In a prospective study conducted in patients undergoing hip replacement surgery, there was no significant difference in exposure to allogeneic blood products between autologous donors and non-donors.[247] In a retrospective study by Jawan *et al.*,[248] performed to compare liver resection patients donating their own blood preoperatively with those not doing so, none of the patients required perioperative transfusion of blood products. Consequently, all predonated blood was discarded. In another retrospective study, performed in knee/hip arthroplasty patients, autologous blood donation was associated with increased perioperative transfusion and the authors suggested that autologous donation may create a 'self-defeating cycle of blood donation followed by blood transfusion'.[249] Autologous blood transfusion may be considered for patients with multiple antibodies (for whom donor blood may be difficult to obtain).

Autologous blood donation increases preoperative anaemia. In a retrospective study of patients scheduled for knee replacement surgery, haemoglobin concentrations before autologous blood donation were compared with those immediately before surgery.[200] The percentage of patients with a haemoglobin concentration in the range of 10–13 g dl^{-1} (at high risk for perioperative transfusion) increased from 26.2% to 55.7%. In the liver resection study by Jawan *et al.*,[248] significantly lower perioperative haemoglobin concentrations were observed in autologous blood donation patients than in non-donors. Another comparative retrospective study reported that patients undertaking autologous blood donation had significantly lower haemoglobin concentrations before surgery than patients not making autologous donations; the authors concluded that 'autologous blood donation induced preoperative anaemia'.[244]

Randomised controlled trials indicate that erythropoietin may be used to increase the proportion of patients able to make autologous blood donations (assuming a minimum haematocrit threshold for making a donation)[228] and to reduce the extent to which autologous blood donation lowers haemoglobin concentration.[250]

One randomised controlled trial assessed prophylactic administration of autologous fresh frozen plasma (FFP) after CPB in patients undergoing coronary artery bypass surgery.[251] This intervention failed to produce significant reductions in transfusion or blood loss compared with administration of hydroxyethyl starch.

Autologous platelet-rich plasma may be superior to autologous whole blood in decreasing transfusion of allogeneic blood products. Farouk *et al.*[252] performed a randomised trial comparing administration of platelet-rich plasma with acute normovolaemic haemodilution in patients undergoing open heart surgery. Platelet-rich plasma produced a significant decrease in transfusion of blood products compared with acute normovolaemic haemodilution.

6.1.3.1 Other possible treatment approaches

Combined use of intravenous iron, erythropoietin, vitamin B_{12}, folic acid, and restrictive transfusion may reduce transfusion requirements. Limited evidence suggests that patients with anaemia might benefit from combination therapy. In a prospective study, patients undergoing total knee replacement received intravenous iron sucrose and, if haemoglobin concentration remained $<$13.0 g dl^{-1}, additional erythropoietin. These measures, together with restrictive transfusion, 'seem to reduce allogeneic blood transfusion', although there was no control group.[215] Retrospective assessment of a similar approach to managing anaemia in hip fracture patients showed a reduction in transfusion compared with oral iron or intravenous iron only.[253] Haemoglobin concentrations 48 h after surgery were higher in the oral iron group, but this difference was not apparent 7 days after surgery.

In a retrospective study, intraoperative cell salvage (ICS) was used together with autologous blood donation in hip surgery patients, and homologous blood transfusion was avoided in all 154 patients.[254] Donation volumes were 800 ml for patients undergoing total hip arthroplasty and 1200 ml for patients undergoing rotational acetabular osteotomy.

6.2 Intra- and postoperative optimisation of macro- and microcirculation

6.2.1 Introduction

Massive bleeding affects delivery of blood to organs and tissues (due to hypovolaemia), as well as the oxygen-carrying capacity of blood (due to anaemia). Because normal haemoglobin concentrations provide a large oxygen carrying capacity, priority goes to intravascular volume replacement with plasma substitutes devoid of red blood cells (RBCs). Transfusion of RBCs is required only when the haemoglobin concentration decreases to levels at which overall nutrient demands cannot be met. This section focuses on rational fluid substitution techniques and anaemia management in patients suffering severe haemorrhage.

6.2.2 Evidence-based medicine and perioperative fluid therapy

Creating reliable and generally acceptable outcome based evidence on perioperative fluid management is currently not feasible due to a lack of controlled studies, the limited representation of clinical scenarios and the absence of a consistent terminology. Several studies have evaluated the impact of perioperative fluid therapy on patient outcomes.[255–268] However, few qualify to serve as a basis for recommendations. The better studies have been performed in abdominal surgery,[256,263–265,268] where perioperative fluid needs may differ considerably from other surgical procedures.[269] Patients at high-risk are often excluded, even if they represent the typical collective.[270] The impact of perioperative fluid management on outcome cannot be isolated from other interventions[271] and only two prospective trials included details of therapeutic strategy beyond fluid therapy.[261,262] Perioperative fluid management must be embedded in a larger perioperative therapeutic concept in order to impact on patient outcome.

6.2.3 Optimising macrocirculation

6.2.3.1 Preload optimisation

Recommendation

We recommend aggressive and timely stabilisation of cardiac preload throughout the surgical procedure, as this appears beneficial to the patient. **1B**

Hypovolaemia decreases cardiac output and tissue oxygen supply. Both the extent and duration of tissue hypoperfusion determine the severity of cellular damage and should be kept to a minimum with timely

volume substitution. Two recent meta-analyses concluded that a goal-directed approach to maintaining tissue perfusion reduces mortality, postoperative organ failure and surgical complications in high-risk surgical patients.[272,273]

Recommendation
We recommend the avoidance of hypervolaemia with crystalloids or colloids to a level exceeding the interstitial space in steady state, and beyond an optimal cardiac preload. **1B**

The relationship between risk and total volume transfused appears to follow a U-shaped curve (infusing too much can be as deleterious as infusing too little).[274] Fluid excess can have a negative impact on cardiac, pulmonary and bowel function, wound healing and water and sodium regulation.[275] Surgery causes inflammation[276] and the corresponding release of mediators causes local tissue oedema.[277] Artificial hypervolaemia predisposes patients to interstitial oedema, which appears to be associated with perioperative mortality.[278]

Recommendation
We recommend against the use of central venous pressure and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimise preload during severe bleeding; dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead. **1B**

To determine the amount of fluid required, high fidelity monitoring is necessary. The monitored variable should predict whether or not a fluid bolus will increase cardiac output.

Central venous pressure (CVP) remains the most widely used clinical marker of volume status, despite numerous studies showing no association between CVP and circulating blood volume.[279] Several studies have demonstrated that dynamic parameters such as stroke volume variation (SVV) or pulse pressure variation (PPV) provide better prediction of fluid responsiveness in mechanically ventilated patients with a normal heart rhythm. Fluid challenges and the leg-raising test represent simple and valid alternatives;[280] no data prove the superiority of substitution regimens guided by SVV or PPV.

The most extensively studied and successfully used method to maximise cardiac preload is the oesophageal Doppler device.[259,281–286]

6.2.3.2 Delayed and low-volume resuscitation techniques

The general implementation of a delayed or low-volume resuscitation protocol for the severely bleeding patient cannot be recommended at this time. However, such a protocol may be applied for specific lesions, provided that surgical control of bleeding is imminent.

6.2.4 Considerations for microcirculation

6.2.4.1 Compartmental fluid dynamics

Basic physiological principles during steady state assume the presence of a cell membrane, quantitatively impermeable to electrolytes, proteins and colloids, and a vascular barrier which retains proteins and colloids, but is freely permeable to electrolytes and other small solutes. Water flows passively across all compartments and distributes according to the amount of osmotically and oncotically active substances. This leads to the following primary distribution pattern: free water evenly across all the compartments (intravascular volume effect negligible); isotonic crystalloids within the extracellular fluid space (intravascular volume effect around 20%); and iso-oncotic colloids and proteins within the intravascular space (intravascular volume effect around 100%).[276,277,287–289] Thus, the infusion of crystalloids has been associated with substantial interstitial oedema (unpublished observations).

6.2.4.2 Crystalloids versus colloids

Recommendation
We suggest the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol based manner. **2C**

Compared with crystalloids, haemodynamic stabilisation with iso-oncotic colloids, such as human albumin and hydroxyethyl starch, causes less tissue oedema. **C**

Losses from the extracellular space occur continuously via perspiration and urinary output. During fasting, these losses are not replaced and substitution is required. Healthy adults perspire around $0.5\,ml\,kg^{-1}\,h^{-1}$, and the corresponding value during major abdominal surgery is $\leq 1\,ml\,kg^{-1}\,h^{-1}$.[290] This loss, together with urinary output, should be replaced. There is no evidence that additional administration of crystalloid preserves organ function.

In healthy patients, stabilisation of cardiac preload with iso-oncotic colloids such as human albumin and hydroxyethyl starch causes less tissue oedema than do crystalloids. It is unclear whether this translates into any clinical outcome benefit. The safety profile of artificial colloids is unconfirmed.

The most important colloid solutions are human albumin, hydroxyethyl starch, gelatin and dextran. The volume effect of gelatin preparations appears inferior to that of starch or albumin preparations.[291–293] However, a recent review concluded that such effects are temporary and do not translate into different clinical outcomes.[292] While side effects of colloids remain a concern, a recent systematic review failed to show any significant safety differences between the available colloids.[294]

6.2.4.3 Chlorine balanced solution

Recommendation
We suggest the use of balanced solutions for crystalloids and as a basic solute for iso-oncotic preparations. **2C**

In balanced crystalloids, metabolic anions (mainly acetate or lactate) are used instead of chloride to establish electroneutrality and isotonicity *in vitro*. Although no outcome benefit has been shown, there is little reason to question the rationale for using balanced solutions.[295]

6.2.4.4 Transfusion triggers

Recommendation

We recommend a target haemoglobin concentration of 7–9 g dl^{-1} during active bleeding. **1C**

It has been demonstrated that acute anaemia (Hb < 5 g dl^{-1}) can be tolerated in healthy individuals, because compensatory mechanisms (predominantly an increase of cardiac output) can ensure sufficient tissue oxygenation.[296]

During bleeding, patients may be less able to tolerate anaemia because the compensatory mechanisms may be impaired. However, it is not known whether the lowest tolerable haemoglobin concentration is determined by volume status. Recent data from patients undergoing surgery and under intensive care indicate that a restrictive transfusion regimen (Hb 7–8 g dl^{-1}) is as effective and as safe as a liberal transfusion regimen (Hb 9–11 g dl^{-1}).[9,297–300] Considering the lack of benefits from higher haemoglobin concentrations, and the potential side effects of transfusing allogeneic blood, haemoglobin concentrations above 9 g dl^{-1} cannot be supported.[4]

It has been speculated that haemoglobin concentration might influence coagulation. At high haemoglobin concentrations, erythrocytes congregate in the inner lumen of blood vessels, resulting in localisation of thrombocytes at the vessel wall, and this may improve clot formation. Furthermore, erythrocytes stimulate thrombin generation, thereby providing material for clot formation.[301] However, no randomised controlled trials have proved that increasing haemoglobin concentration above 9 g dl^{-1} reduces bleeding or the number of blood transfusions.

6.2.4.5 Oxygen fraction

Recommendation

We recommend that inspiratory oxygen fraction should be high enough to prevent arterial hypoxaemia in bleeding patients, while avoiding extensive hyperoxia ($PaO_2 > 26.7$ kPa [200 mmHg]). **1C**

The use of high inspiratory oxygen fractions during artificial ventilation (hyperoxic ventilation, HV) is traditionally advised for emergencies on the basis that severe arterial hypoxaemia potentially endangers oxygen delivery. However, it has been demonstrated that the side effects of HV (e.g. vasoconstriction) may worsen patient outcomes.[302,303] Overall, current evidence supports the use of HV to achieve physiological arterial oxygen partial pressures during haemorrhagic shock.

6.2.4.6 Monitoring tissue perfusion

Recommendation

We recommend repeated measurements of a combination of haematocrit/haemoglobin, serum lactate, and base deficit in order to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. These parameters can be extended by measurement of cardiac output, dynamic parameters of volume status (e.g. stroke volume variation, pulse pressure variation) and central venous oxygen saturation. **1C**

There is no easily applicable tool for monitoring blood volume in a clinical setting. Consequently, surrogate parameters (e.g. haematocrit/haemoglobin, central venous pressure, pulmonary capillary wedge pressure, stroke volume variation, pulse pressure variation, serum lactate concentration, base deficit) are used. Some of these parameters have been demonstrated to be inappropriate, such as central venous pressure and pulmonary capillary wedge pressure, while others require specific monitoring tools which are not widely available, including stroke volume variation and pulse pressure variation with special monitors.

Due to low sensitivity and specificity, haematocrit and haemoglobin concentration should not be used as exclusive measures to monitor the extent of acute blood loss.[304,305] However, since haemoglobin concentration is one important determinant of systemic oxygen delivery, it should be monitored regularly.

Serum lactate concentration and base deficit reflect global tissue perfusion and oxygenation in haemorrhagic shock. Although both can be influenced by many different factors, their concentrations can be used to determine severity of haemorrhagic shock, guide substitution and transfusion protocols[306,307] and potentially predict survival.[308] However, it has not yet been shown whether the outcome of severe bleeding can be improved if volume resuscitation is guided by serum lactate concentration and base deficit.[309]

Central venous oxygen saturation ($ScvO_2$) is used in sepsis to guide volume therapy and other measures to optimise oxygen delivery.[310] Although it has been demonstrated that $ScvO_2$ reflects blood loss in the early stages of haemorrhagic shock,[311] circulation is centralised during severe haemorrhage, which raises $ScvO_2$. Therefore, $ScvO_2$ values during severe haemorrhage must be interpreted cautiously.[312]

6.3 Transfusion of labile blood products

6.3.1 Infectious risk of allogeneic blood components

Recommendation

We recommend that all countries implement national haemovigilance quality systems. **1C**

Although tremendous progress has been made regarding the safety of blood components, there remains a residual

risk of transfusion-related infection.[313] Most transfusion services in Europe and the USA require that all donations are screened for hepatitis B and C viruses (HBV; HCV), human immunodeficiency virus (HIV) and syphilis.[314–317] Universal testing for other infectious agents such as West Nile Virus, malaria, Chagaz disease and human T-cell lymphotropic virus (HTLV) is not justified because of their restricted geographical distribution; instead, donor screening is employed. Potential donors are asked questions on travel history, drug abuse, sexual behaviour, etc; however, residual risks remain. There is also a risk that laboratory testing of donated blood is not effective. There is usually a period during which the donation is infectious but will screen negative because the infectious marker is not present at detectable levels. Shortening of this 'window period' is a major target of all screening programmes.

In addition to known infectious agents, there is also the threat of new or emerging pathogens.[313] Due to increased travel and spread of mosquitoes, the most important emerging threats are the mosquito borne Dengue, Chikungunya and Zika viruses.[318]

Bacterial contamination is another issue of transfusion practice. Since the introduction of disposable collection systems, the incidence of bacterial contamination has decreased dramatically. However, platelets, which are stored at room temperature and suspended in plasma, still present a significant risk. The greatest risk of contamination occurs during collection, because bacteria are present on the donor's skin.[319] Disinfection techniques have improved, and small sideways collectors used to collect the first 30 ml of donated blood reduce the contamination risk. Additional measures include the use of closed systems and improvements in processing area hygiene.

Most countries have developed a national haemovigilance system to identify adverse outcomes of transfusion. Introduced in 1996, the UK Serious Hazards of Transfusion (SHOT) scheme involves compulsory reporting of all transfusion-related incidents. The latest SHOT report (2009) demonstrated a tremendous reduction in serious outcomes compared with the first report (1996).[320] However, links between infection and transfusion are not always made.

Recommendation
We recommend a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products. **1A**

One of the most effective ways to reduce transfusion related infection is to introduce a restrictive transfusion protocol, i.e. transfuse only what is really necessary (RBCs, plasma or platelets) and only when it is really necessary.

The Transfusion Requirements in Critical Care (TRICC) multicentre randomised controlled trial compared restrictive transfusion (Hb concentration maintained at 7–9 g dl^{-1}) with liberal transfusion (Hb concentration maintained at 10–12 g dl^{-1}); 30-day mortality was higher with liberal transfusion.[321] A recent Cochrane review of RBC transfusion triggers included 17 RCTs.[8] A lower RBC transfusion trigger reduced postoperative infection by 24%, with no adverse effects on mortality, cardiac morbidity or length of hospital stay. Transfusion in acute coronary syndrome has been associated with increased mortality,[322] except in the elderly where it reduces fatality if the haematocrit is below 30%.[323]

Recommendation
We recommend photochemical pathogen inactivation with amotosalen and UVA light for platelets. **1C**

Pathogen inactivation kits have recently been licensed for plasma and platelets, but not for RBCs. Such technology is probably most important for new and emerging infectious threats or in situations in which testing is only partially effective (e.g. bacterial contamination of platelet products).

Solvent and detergent (SD) was the first pathogen inactivation technique, introduced for plasma in the early 1990 s.[324] The process is based on disruption of the viral envelope but is only effective against lipid-enveloped viruses and is not applicable for use with RBCs or platelets.

More recently, the combination of photosensitisers and white or ultraviolet light has been developed to act at the nucleic acid level.[325] The principle of this approach is that viral and bacterial pathogens (except prions) need genetic material to be viable, whereas therapeutic blood components do not. The Intercept Blood System (Cerus Corporation, Concord, CA) for platelets and plasma uses photoactive amotosalen to irreversibly block the replication of DNA and RNA. The Systolic Blood Pressure Intervention Trial (SPRINT) examined the therapeutic efficacy and safety of platelets treated with amotosalen and ultraviolet light.[326] This RCT showed that the use of pathogen-inactivated platelets is not associated with increased bleeding and confirmed a lack of either toxicity or neoantigen formation associated with this photochemical process.[326]

Another photoinactivation method applied to plasma is methylene blue combined with visible light. Few RCTs have assessed this method, and there are concerns over reduced efficacy of methylene blue treated plasma in patients with thrombotic thrombocytopaenic purpura.[327]

Photoinactivation is less applicable to RBCs because of their high optical density, which impairs penetration of photoactive molecules. Nevertheless, research with riboflavin is ongoing.

Recommendation
We recommend that labile blood components used for transfusion are leukodepleted. **1B**

The infectious risk of leukocyte-mediated viruses (cytomegalovirus [CMV], HTLV, HIV) may be reduced by prestorage removal of leukocytes from blood components. For RBCs, this can be achieved by using dedicated filters, while for platelet products, leukocytes are removed during the collection process via apheresis. Third-generation leukocyte depletion filters appear effective in preventing primary CMV infection in neonates, adult cancer patients and bone marrow transplant patients. Leukodepletion does not remove all leukocytes, but there is evidence that CMV seronegative and leukoreduced blood components are equivalent, provided that $\leq 5 \times 10^6$ white cells remain in the product transfused.[328]

Universal leukodepletion of blood components was introduced in the UK in 1998 on the basis that it reduces the risk of variant Creutzfeldt-Jacob disease (vCJD) transmission.[329]

Another benefit of prestorage leukodepletion is prevention of febrile non-haemolytic transfusion reactions (FNHTRs). These are the most frequent adverse reactions following transfusion of blood components, with an incidence of 1% with non-leukodepleted RBCs and 5–10% with platelets.[330] The main cause of FNHTRs is antibodies in the recipient being directed against antigens on the donor's white cells and platelets.[331] Leukoreduction of transfused blood components to $<5 \times 10^6$ leukocytes per unit has been shown to significantly reduce the occurrence of FNHTRs.[329,332]

6.3.2 Immunological complications of blood transfusion

The SHOT report is a haemovigilance data collection system involving all UK hospitals. Since it began, 6653 transfusion-related adverse events have been recorded. In the first SHOT report (1996–1997) there were 141 reports, 36 cases of major morbidity and 12 deaths, representing a serious outcome percentage of 34% (48/141). By 2009, the serious outcome percentage had decreased to 6.7% (86/1279). Two hundred and eighty two reports (22%) were attributable to incorrect blood component transfusion (e.g. wrong ABO and Rh group).[320] It is estimated that approximately 1 in 30 000 transfused RBC units are ABO incompatible and that around 1 in 500 000 deaths are due to ABO incompatibility. This is ten-fold higher than the risk of acquiring HIV infection by transfusion in the UK.[317] Other immune mediated causes of transfusion-related morbidity and mortality identified by SHOT include haemolytic transfusion reactions, FNHTRs, allergic and anaphylactic reactions, transfusion-related acute lung injury (TRALI) and transfusion-associated graft-versus-host disease (TA-GVHD).

Recommendation

We recommend that blood services implement standard operating procedures for patient identification and that staff be trained in early recognition of, and prompt response to, transfusion reactions. **1C**

Haemolytic transfusion reactions (HTRs) are typically caused by transfusion of RBCs carrying antigens to which the recipient has significant alloantibodies. The vast majority of cases are attributable to bedside clerical/procedural errors, either when taking samples for pre-transfusion screening or before the administration of the blood component.[333]

The pathogenesis of HTRs may be related to complement activation after IgM antibodies have been fixed (severe acute HTRs), or to IgG antibodies (e.g. anti-D, anti-K) in patients who have been sensitised either by pregnancy or by previous transfusion (less severe acute HTRs; approximately 1 in 25 000 transfused units of RBCs).[334] Onset of HTRs can be delayed by approximately 1 week following transfusion, by anamnestic or secondary immune responses in previously primed patients.

The first signs of both acute and delayed HTRs are fever and chills.[335] Hypotension, tachycardia, nausea and vomiting, loin and chest pain, and renal failure may be associated with acute HTRs or, less commonly, with delayed HTRs. Anaesthesia may mask the typical symptoms of renal failure and red cell destruction may be noted by the presence of haemoglobinuria and excessive bleeding because of disseminated intravascular coagulation. Haemoglobinaemia, haemoglobinuria, jaundice and DIC may also occur with acute HTRs, in relation to intra- or extravascular haemolysis.

The most frequent cause of intravascular HTRs is ABO incompatibility attributable to procedural errors. Most deaths occur with transfusion of group A or group B to group O recipients.

Occasionally HTRs may be associated with transfusion of plasma or even platelets. Here, transfusion of group O plasma containing antibodies against A or B antigens on the recipient's RBCs leads to haemolysis.

Rarely, incompatibility between RBCs from one donor and the plasma from another donor causes haemolysis in the recipient (interdonor incompatibility).

The American Association of Blood Banks guidelines recommend that if an HTR is suspected, transfusion must be stopped immediately.[330] This is because the severity of haemolysis is related to the volume of incompatible blood transfused. Treatment should be guided by the clinical manifestations. For mild symptoms, careful observation may suffice, but severe reactions demand vigorous therapy. For example, exchange transfusion may be lifesaving in cases of ABO incompatibility and severe haemolysis. Renal failure may be prevented by maintaining urine output with fluids and diuretics. Pressure support may be needed in the presence of hypotension

and shock, while DIC should be managed according to local protocols.

Febrile non-haemolytic transfusion reactions (FNHTRs) are defined as an increase in body temperature of $\geq 1^{\circ}C$ occurring in association with the transfusion of blood components and not explained by other aspects of the patient's medical condition. Chills, rigor and discomfort may be present and usually respond well to antipyretic agents. Because fever is present in other transfusion reactions, such as acute HTR, TRALI and bacterial contamination, diagnosis of FNHTR is made by exclusion. If in doubt, a direct antiglobulin test should be performed and concentrations of free haemoglobin should be assessed.

Allergic and anaphylactic reactions develop as a type 1 hypersensitivity response to plasma proteins present in transfused blood components, meaning that an immediate allergic reaction follows any subsequent contact with the antigen to which the recipient has been previously sensitised. Crosslinking of antigen with surface IgE stimulates degranulation of the mast cells.[336] These cells are usually distributed in the skin and in the mucosa of gastrointestinal and respiratory tracts, hence the symptoms of itching, flare reactions, bronchoconstriction, nausea and vomiting, diarrhoea and abdominal cramps. Benign skin allergic responses to transfusion of plasma-containing blood components, including RBCs and platelets, manifest as local erythema, urticaria and pruritus in 1–3% of cases. Anaphylactic transfusion reactions are much less frequent (1 in 20 000–400 000 units transfused). In the event of anaphylaxis, the infusion should be stopped immediately and adrenaline administered. Circulatory and respiratory support may be indicated. Diagnosis of an anaphylactic transfusion reaction must be made by demonstrating deficiency of IgA and presence of IgG anti-IgA in the recipient. Patients should subsequently receive blood components from an IgA-deficient donor population or autologous transfusion.[337]

Recommendation

We recommend that multiparous women be excluded from donating blood for the preparation of FFP and for the suspension of platelets in order to reduce the incidence of TRALI. **1C**

Transfusion-related acute lung injury (TRALI) is potentially life-threatening and occurs within 6 h of transfusion of plasma containing blood products.[338] Patients with TRALI commonly present with fever, chills, hypotension, dyspnoea, non-productive cough and cyanosis. Severe hypoxaemia is common, so many patients need supplemental oxygen and mechanical ventilation. Because there is no pathognomonic feature or diagnostic test available for TRALI, diagnosis is by exclusion. Most cases improve within 2–3 days if adequate respiratory and circulatory support is provided. The fatality rate from TRALI is 5–8%.

The 2009 SHOT report includes 21 cases of TRALI out of the total of 1279 reported adverse incidents.[320] However, mild forms of TRALI may go unnoticed and severe cases may be attributed to factors such as circulatory overload; therefore, the true incidence is probably underestimated.

In the UK and Belgium, donations from multiparous women are excluded for the preparation of FFP and platelets. This strategy appears to be beneficial in reducing the incidence of TRALI.[338–340]

In France, HLA antibody screening of previously pregnant female donors has been found acceptable in case of shortage.

Recommendation

We recommend that all RBC, platelet and granulocyte donations from first-or second-degree relatives be irradiated even if the recipient is immunocompetent, and all RBC, platelet and that granulocyte products be irradiated before transfusing to at-risk patients. **1C**

Transfusion-associated graft-versus-host disease (TA-GVHD) is a potential complication if the transfused blood component contains viable T-lymphocytes and there is disparity in HLA-antigens between donor and recipient.[341] The main risk factors are: congenital immunodeficiency disorders; Hodgkin's disease; *Erythroblastosis fetalis* and premature birth (neonates); intrauterine transfusion; stem cell transplants; donations from first- or second-degree relatives; HLA-matched cellular products; and recipient-donor pairs from genetically homogeneous populations.

The immune cells of immunocompetent recipients far outnumber donor T-lymphocytes, so the latter are usually eliminated by a host-versus-graft response. However, if functional T-lymphocytes are transfused from a donor who is homozygous for one of the recipient's haplotypes, the recipient may fail to recognise them as foreign. The donor T-lymphocytes recognise the host as foreign, proliferate and cause TA-GVHD. Because the onset of clinical symptoms is delayed for 8–10 days after transfusion, careful monitoring is warranted. Typical features of TA-GVHD include fever, maculopapular skin rash affecting the palms, diarrhoea and hepatitis. Infection leads to deterioration in health, with death occurring within 1 month in over 90% of cases.[337] The quickest way to diagnose TA-GVHD is by skin biopsy; histological changes including basal cell layer degeneration with vacuolisation, dermal epithelial layer separation and bulla formation are evident. It is useful also to establish the persistence of donor T-lymphocytes in the recipient's circulation or tissues, using DNA analysis.[342–344] However, their presence alone does not necessarily indicate TA-GVHD because donor lymphocytes can persist after transfusion. Because concomitant medical conditions may conceal TA-GVHD symptoms, the incidence is underestimated.

There is no effective treatment of TA-GVHD. Prevention is by removing donor lymphocytes or by destroying their proliferative capacity. Leukodepletion to less than 10^6 white cells per unit does not eliminate the risk. However, since the introduction of universal leukodepletion in the UK, a significant decrease in TA-GVHD cases has been observed and the 2009 SHOT report (UK) does not record any cases.[320] The mainstay of prevention remains gamma irradiation of cellular blood components to prevent donor leukocyte proliferation.[345] However, because of the low incidence of TA-GVHD in immunocompetent recipients receiving blood components from unrelated donors, gamma irradiation is not warranted on a routine basis.

Recommendation

We recommend the transfusion of leukocyte reduced RBC components for cardiac surgery patients. **1A**

The concept of transfusion-related immunomodulation (TRIM) explains laboratory immune aberrations perceived after blood transfusion. Initially, TRIM only encompassed the effects of allogeneic transfusion attributable to immunomodulation (e.g. cancer recurrence, postoperative nosocomial infection, virus activation), but recently the potential effects of proinflammatory mechanisms (e.g. multiple organ failure, mortality) were added.[346]

Increased cancer recurrence after blood transfusion has been shown in *in vitro* studies, animal models and observational studies.[347] However, a randomised controlled study did not find any difference in colorectal cancer recurrence after 2 and 5 years.[348] The true effect of TRIM on cancer recurrence remains to be demonstrated in a sufficiently powered RCT.

The influence of allogeneic blood transfusion on postoperative nosocomial infections has been investigated in several meta-analyses.[349–352] However, because of differences in surgical patients, definitions for postoperative infection and type of transfused blood components, the evidence is inconclusive.

Higher mortality rates among transfused versus non-transfused patients can generally be explained by patient selection, because anaemia is an independent risk factor. However, in cardiac surgery, increased postoperative infection attributable to TRIM has been demonstrated among patients receiving leukocyte containing RBCs compared with those receiving leukocyte reduced RBCs.[353] In the same RCT, inhospital mortality and length of hospital stay were also increased in patients receiving leukocyte containing RBCs. A subsequent RCT conducted by the same authors confirmed the results of their first trial.[354]

6.3.3 Preparation of labile blood components

Because very few indications remain for whole blood transfusion, it is now common for plasma, platelets, RBCs, granulocytes and stem cells to be collected by apheresis. For this technique, one (or more) component(s) are collected from the donor by centrifugation and the unwanted components are returned to the donor's circulation. The main advantage of apheresis is the collection of more than one dose of a selected component per donation, reducing the number of donors to whom recipients are exposed.

For preparation of FFP at the Belgian Military Hospital, the plasma units are weighed and then subjected to inline leukodepletion by gravity filtration. Pathogen inactivation is performed using the Intercept Blood System (amotosalen and ultraviolet light). Each unit (approximately 200 ml) is frozen at −75°C, before storage at −85°C for up to 1 year. All FFP units undergo quality control, including determination of factor VIII (FVIII) and protein concentrations, as well as leukocyte, RBC and platelet counts.

Leukodepletion of platelet components takes place during the last step of separation. After a 2 h collection period, aliquots of plasma and suspension liquid are added to produce two platelet units, each containing approximately 4×10^{11} platelets. Each platelet unit undergoes pathogen inactivation by amotosalen and ultraviolet light.[325] Amotosalen is removed by filtration before storage at 20–22°C (shelf life: 5–7 days). Quality control involves measuring volume and pH, as well as platelet, RBC and leukocyte counts. Other techniques used for platelet production are the 'buffy coat' method favoured in Europe and the platelet-rich plasma (PRP) technique used in North America.[355]

After their separation from whole blood, RBCs are suspended in Nutricel additive solution (Bayer AG, Leverkusen, Germany). Nutricel provides a shelf life of 49 days, 7 days longer than the more commonly used SAGM solution. Promptly after collection, the units are leukodepleted by gravity filtration. Quality control, performed on 1 in 20 units, includes determination of blood group, haemoglobin concentration and haematocrit, leukocyte count, lactate dehydrogenase (LDH), 2,3-diphosphoglycerate (2,3-DPG), adenosine triphosphate (ATP), potassium and lactate concentrations, and pH. European guidelines suggest RBC units produced by apheresis should have a haematocrit of 50–70% when suspended in SAGM solution and 55–70% when Nutricel is used.

6.3.4 Cell salvage

Recommendation

We recommend the routine use of red cell saving which is helpful for blood conservation in cardiac operations using CPB. **1A**

In light of the potential adverse effects of transfusing allogeneic blood components, the ever increasing cost and the shrinking donor pool, strategies to reduce perioperative blood transfusion are being developed. Intraoperative cell salvage (ICS) has been proposed as a

key method for reducing perioperative blood transfusion.[356]

In order to be cost-effective, an initial 'stand-by' setup using only a sterile reservoir, a double lumen suction catheter and a solution for anticoagulation is required. Once sufficient wound blood has accumulated, the main washing device is installed. Several devices are available and all use the principle of centrifugation to separate RBCs from plasma and the wash solution. After priming the system with 100–200 ml of heparin solution (30 IU ml^{-1}), 1), the flow is adjusted to an anticoagulant:blood ratio of 1:5 to 1:7.[357] Shed blood is aspirated, anticoagulated at the suction catheter tip and stored in a sterile reservoir equipped with a microaggregate filter. Anticoagulated and filtered wound blood is pumped into the centrifuge for RBC separation. The RBCs are then washed and suspended in saline to obtain a haematocrit of 50–70%. Leukocytes are removed with the buffy coat to varying degrees.[358–361]

ICS should be considered for all operations with significant likely blood loss, i.e. >20% of the patient's estimated blood volume.[362] Cardiac surgery using CPB is a major indication.[363] In this setting, significantly reduced blood loss and transfusion requirements have been demonstrated, with decreased complication rates and reduced systemic inflammation related to removal of most but not all cytokines from suctioned blood. Routine use of red cell saving is recommended by the American Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists for blood conservation in cardiac operations using CPB.[364] However, ICS is contraindicated in patients with infection or malignancy and in situations in which the blood is exposed to topical clotting agents (e.g. fibrin glue or any other thrombin containing compound).

Recommendation

We recommend against the routine use of intraoperative platelet-rich plasmapheresis for blood conservation during cardiac operations using CPB. **1A**

Platelet dysfunction is a major factor in CPB-induced coagulopathic bleeding. It would therefore seem reasonable to remove platelet-rich plasma from circulating whole blood before starting CPB, for infusion at the end of surgery. However, a meta-analysis found that intraoperative platelet-rich plasmapheresis was not beneficial.[365] The process is labour intensive and technical mistakes might be harmful.[366]

6.3.4.1 Other surgical settings

Recommendation

We recommend the use of red cell salvage in major orthopaedic surgery because it is useful in reducing exposure to allogeneic red blood cell transfusion. **1A**

In off-pump cardiac surgery, red cell salvage is recommended. Another area in which ICS has proved to be beneficial is in major orthopaedic surgery, such as hip replacement, spinal operations and repair of pelvic fractures.[357,367,368] Other indications for ICS include abdominal aortic aneurysm repair,[369] hepatectomy, radical prostatectomy, nephrectomy, cystectomy and emergency medicine (e.g. major abdominal and/or thoracic trauma).[370]

Definite contraindications to ICS include the intraoperative use of sterile water, hydrogen peroxide or alcohol, as these substances would induce severe RBC haemolysis.[371] When shed blood is potentially contaminated with bacteria, amniotic fluid or malignant cells, the decision to use ICS should be made on a case-by-case basis.[356]

In cancer surgery, there is concern about the risk of reinfusing malignant cells, which could cause metastases. Certainly, aspiration of blood from close to the tumour site should be avoided. Leukodepletion may reduce the risk, but residual cancer cells after filtration are unacceptable because it has been demonstrated that one single tumour cell is capable of causing metastasis.[372] Despite these considerations, studies in urological cancer surgery have shown ICS not to affect biochemical recurrence or long term survival.[373,374] In 2008, the UK National Institute of Health and Clinical Excellence (NICE) approved the use of ICS in urological malignancy surgery.[375] It is well known that DNA proliferation of radiosensitive tumour cells can be eradicated by gamma irradiation.[376,377] Irradiation has also been shown not to impair RBC quality.[376] Therefore, irradiation of intraoperatively salvaged wound blood could potentially increase the acceptance of ICS in cancer surgery.

Recommendation

We recommend that intraoperative cell salvage is not contraindicated in bowel surgery, provided that initial evacuation of soiled abdominal contents and additional cell washing are performed, and that broad-spectrum antibiotics are used. **1C**

Contamination of the surgical field (e.g. bowel surgery, penetrating abdominal trauma or infected wounds) has typically been considered as a contraindication to ICS. However, the literature indicates no difference in infection rate after laparotomy for abdominal trauma in patients receiving allogeneic blood components or cell salvaged blood. There also seems to be no correlation between microbial organisms grown from cell salvaged blood and those involved in postoperative pneumonia, bacteraemias or urinary tract infections. An RCT in patients undergoing laparotomy for abdominal injuries demonstrated that ICS significantly reduced allogeneic blood usage without increasing postoperative infection or mortality rate.[378] Consequently, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines state that, in the setting of bowel surgery, red cell salvage is indicated, provided that initial evacuation of the soiled abdominal contents and additional cell

washing are performed, and that broad-spectrum antibiotics are used.

During the peripartum period, shed blood can be contaminated with amniotic fluid and fetal blood, so reinfusion carries a theoretical risk of amniotic fluid embolism. However, with no proven case of this, NICE has approved the use of cell salvage in obstetrics.[379] Leukodepletion filters are advocated because their use reduces amniotic fluid contamination,[380] but the resulting reduction in reinfusion speed must be considered.

6.3.5 Storage lesions

Recommendation

We recommend that RBCs up to 42 days old should be transfused according to the first-in, first-out method in the blood services to minimise wastage of erythrocytes. **1C**

The legal maximum period for storing RBCs is 42 days. Biochemical and biomechanical modifications occurring during prolonged storage are described as storage lesions.[381] During storage of RBCs, lactic acid accumulates in the blood bag and degrades 2,3-DPG.[382] This increases the oxygen affinity of haemoglobin, meaning that less oxygen is delivered to tissues. After storage of RBCs for 42 days, the majority of 2,3-DPG is degraded. Although half of it recovers *in vivo* within 24 h after transfusion,[383] this might not be fast enough for critical patients needing immediate restoration of oxygen delivery.[384] In addition, ATP content is reduced in stored RBCs, resulting in morphological changes[385] which cause changes in blood viscosity. Membrane remodelling may lead to IgG binding and accelerated erythrocyte destruction.[386] A recent review by Kim-Shapiro[387] hypothesises that storage-associated RBC fragility causes the release of free haemoglobin, which consumes nitric oxide, a key player in blood flow regulation and inflammation.

Several prospective and retrospective studies have attempted to link prolonged storage duration of RBCs with adverse clinical outcome,[388–391] but the results are inconclusive. A recent meta-analysis found a lack of support for the suspicion that transfusion of 'old' RBCs increases morbidity and mortality.[392]

Alfano and Tarasev[393] reported that erythrocyte membrane fragility correlated well with transfusion efficacy and that mechanical fragility differed between RBCs of the same age. These findings suggest that the traditional blood service inventory management founded on the first-in, first-out method could be replaced by an approach taking into account the quality of the RBCs. It would also become possible to prioritise the best performing RBC units for the sickest patients. Recently, Raval *et al.*[394] demonstrated that mechanical fragility is independent of age but correlates with storage solution and donor gender. Vincent *et al.*[395] suggest that RBC units which may be ineffective for some patients could nonetheless be beneficial for others.

7 COAGULATION MANAGEMENT

7.1 Indications, contraindications, complications and doses

7.1.1 Introduction

Many treatment protocols for perioperative bleeding use fixed ratios of allogeneic blood products. However, transfusion of allogeneic blood products increases morbidity and mortality, and fixed ratios might not improve outcomes.[141,396–408] We searched for evidence on the use of fibrinogen concentrate, cryoprecipitate, factor XIII (FXIII) concentrate, recombinant activated factor VII (rFVIIa), PCC, vitamin K, desmopressin (DDAVP), aprotinin and tranexamic acid in severe perioperative bleeding.

7.1.2 Fibrinogen concentrate

Recommendation

We recommend treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen concentrations or function. **1C**

We recommend that a plasma fibrinogen concentration $<1.5–2.0\,g\,l^{-1}$ or ROTEM/TEG signs of functional fibrinogen deficit should be triggers for fibrinogen substitution. **1C**

We suggest an initial fibrinogen concentrate dose of $25–50\,mg\,kg^{-1}$. **2C**

In severe bleeding, fibrinogen reaches critical concentrations early,[36,409] and haemorrhagic tendency is increased when fibrinogen concentration is $<1.5–2.0\,g\,l^{-1}$.[36,85,114,182,409–414]

Studies have consistently shown that fibrinogen can increase clot firmness,[124,125,415–429] and data on the efficacy of fibrinogen concentrate in acquired fibrinogen deficiency are increasing. In three randomised trials and two prospective cohort studies, fibrinogen concentrate optimised coagulation, reduced perioperative bleeding and significantly reduced transfusion.[116,117,430,431] Furthermore, in cardiac surgery, first-line therapy with fibrinogen concentrate and PCC based on POC testing has been associated with decreased transfusion requirements, decreased incidence of thromboembolic events and reduced mortality.[119,120]

7.1.3 Cryoprecipitate

Recommendation

We suggest that the indication for cryoprecipitate is lack of available fibrinogen concentrate for the treatment of bleeding and hypofibrinogenaemia. **2C**

In contrast to cryoprecipitate, freeze dried fibrinogen concentrate offers standardised fibrinogen content, faster reconstitution and improved efficacy.[432,433] In addition,

the risks of pathogen transmission and immune-mediated complications are reduced with fibrinogen concentrate.[434,435]

7.1.4 Factor XIII

Recommendation

In cases of ongoing or diffuse bleeding and low clot strength despite adequate fibrinogen concentrations, it is likely that FXIII activity is critically reduced. In cases of significant FXIII deficiency (i.e. <60% activity), we suggest that FXIII concentrate (30 IU kg^{-1}) can be administered. **2C**

Clinical studies have shown an increased bleeding tendency in surgical patients with FXIII activity <60%.[410,413,436–442] However, more data are needed on the effect of FXIII concentrate on bleeding and transfusion requirements.[418,443–448]

7.1.5 Prothrombin complex concentrate

Recommendation

We recommend that patients on oral anticoagulant therapy should be given PCC and vitamin K before any other coagulation management steps for severe perioperative bleeding. **1B**

We suggest that PCC (20–30 IU kg^{-1}) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients. **2C**

PCC is recommended for acute reversal of oral anticoagulation.[449,450] Some centres also administer PCC in cases of massive bleeding and prolonged clotting times,[125,398] although it must be acknowledged that for perioperative bleeding, the data are very limited. Animal trials have shown that PCC can reduce blood loss,[451–456] and two retrospective analyses have shown benefit in patients with bleeding complications.[457,458] Other animal studies have shown conflicting results.[459] A mean dose of 30 IU kg^{-1} increased normalised PT in patients with reduced coagulation activity.[460]

Animal studies suggest that PCC administration might be associated with an increased risk of thromboembolic complications or DIC.[423,461] Vitamin K is required for the synthesis of factors II, VII, IX, and X, and proteins C, S and Z. These factors might be decreased in patients on oral anticoagulant therapy, those with severe malnutrition or severe liver disease, or in newborns. PCC should be administered in these cases of acute severe surgical bleeding.[119,120,449,450]

7.1.6 Recombinant activated factor VII

Recommendation

We suggest that off-label administration of rFVIIa can be considered for bleeding which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails. **2C**

Recombinant FVIIa is licensed for the treatment of patients with haemophilia and inhibitory antibodies, or Glanzmann thrombasthenia.[462] There is conflicting evidence about the use of rFVIIa in surgical bleeding; reduced blood loss and transfusion requirements have been reported,[463–466] while some randomised clinical trials have failed to show a benefit. A recent meta-analysis of patients undergoing liver surgery did not find any benefit from prophylactic rFVIIa.[467] A Cochrane analysis concluded that prophylactic rFVIIa reduced blood loss and transfusion requirements in non-haemophilic patients, while mortality did not change. However, there was also a trend towards increased thromboembolic complications with rFVIIa.[468,469]

Recombinant FVIIa should be administered before haemostasis is severely compromised.[470] The optimum dose is 90–120 μg kg^{-1}, and this can be repeated. Hypofibrinogenaemia,[471] thrombocytopaenia, hypothermia, acidosis and hyperfibrinolysis[45,472] should all be treated before rFVIIa is used.

7.1.7 Antifibrinolytics and tranexamic acid

Recommendation

We recommend the consideration of tranexamic acid (20–25 mg kg^{-1}). **1A**

The efficacy of antifibrinolytics has been well studied in patients undergoing elective surgical procedures.[473–477] A large meta-analysis found that tranexamic acid provides a similar reduction in perioperative transfusion to that seen with aprotinin, but with improved safety.[478–480] Tranexamic acid doses of up to 25 mg kg^{-1} are usually recommended; these can be repeated or followed by continuous infusion (1–2 mg kg^{-1} h^{-1}).

An analysis of tranexamic acid use in 20 211 trauma patients showed that it improves survival rates by approximately 10%.[481]

7.1.8 Aprotinin

Aprotinin is no longer available. Aprotinin was withdrawn from the market because of safety concerns.

7.1.9 Desmopressin (DDAVP)

Recommendation

We suggest the use of DDAVP under specific conditions (acquired von Willebrand syndrome). There is no convincing evidence that DDAVP minimises perioperative bleeding or perioperative allogeneic blood transfusion in patients without a congenital bleeding disorder. **2B**

A Cochrane analysis showed that desmopressin does not significantly reduce the risk of exposure to allogeneic RBC transfusion. In patients undergoing liver resection,

desmopressin has no effect on transfusion requirement[482,483]

In cardiovascular surgery, desmopressin has been shown to reduce postoperative blood loss in patients with severe aortic valve stenosis undergoing aortic valve replacement.[183] In contrast, desmopressin was not effective in patients undergoing CABG who were previously treated with aspirin.[484,485]

7.2 Correction of confounding factors

7.2.1 Correction of temperature, pH, Ca^{2+}

7.2.1.1 Introduction

Hypothermia and acidosis each induce coagulopathy. A core temperature of $\leq$34°C inhibits thrombin generation, fibrinogen synthesis and platelet function, and increases fibrinolysis. Acidosis (pH $\leq$ 7.1) inhibits thrombin generation and platelet function, while accelerating fibrinogen degradation. Reversal of acidosis does not correct acidosis-induced coagulopathy. The positively charged Ca^{2+} enhances fibrin polymerisation, coagulation factor activity and platelet activity.

Recommendation

We recommend maintaining perioperative normothermia because it reduces blood loss and transfusion requirements. **1B**

A meta-analysis found that even mild hypothermia (<1°C below normal) increases blood loss by approximately 16% and relative risk of transfusion by approximately 22% in surgical patients.[486] Intraoperative maintenance of normothermia has been shown in plastic surgery to support normal coagulation.[487] In hip arthroplasty, aggressive intraoperative warming (tympanic membrane maintained at 36.5°C) reduces perioperative blood loss compared with conventional warming (36°C).[488] However, in healthy, anaesthetised adults, reduction of body temperature to 32°C induced only minor effects on coagulation.[489] Hypothermic effects may go undetected, because coagulation tests are typically performed at 37°C.

A pig model has shown that hypothermia (32°C) delays onset of thrombin generation (FVIIa/TF pathway) without affecting late thrombin generation (propagation phase). In this study, acidosis (pH 7.1) slightly inhibited early thrombin generation and significantly impaired late thrombin generation.[490]

Recommendation

We suggest that rFVIIa may be used in treatment of patients with hypothermic coagulopathy. **2C**

While pH correction alone cannot immediately correct acidosis-induced coagulopathy, we recommend that pH correction should be pursued during treatment of acidotic coagulopathy. **1C**

We recommend that rFVIIa should only be considered alongside pH correction. **1C**

A pH decrease from 7.4 to 7.0 can reduce FVII activity *in vitro* by >90% and FVII/TF activity by >60%.[491] Other *in vitro* data show rFVIIa sensitivity to temperature as well as pH.[492] Addition of rFVIIa *in vitro* improves clot reaction times and clot formation rates in mild–moderate, but not severe, hypothermia.[493] In adult surgical patients, rFVIIa may be less effective in acidotic coagulopathy.[494] Conversely, rFVIIa efficacy was reported in another study to be affected by volume expansion but not acidosis or hypothermia.[495]

In thromboelastometric studies of healthy volunteers, hypothermia-induced coagulopathy was exacerbated by acidosis, whereas acidosis without hypothermia had no significant effects on coagulation. Thromboelastometry performed at 37°C may therefore overestimate the integrity of coagulation for patients experiencing hypothermia and acidosis.[496]

A study in pigs showed that acidosis-induced depletion of plasma fibrinogen concentration and platelet count is not reversed by neutralisation of pH with bicarbonate.[497]

Recommendation

We suggest that calcium should be administered during massive transfusion if Ca^{2+} concentration is low, in order to preserve normocalcaemia ($\geq$0.9 mmol l^{-1}). **2B**

In a cohort study, the nadir of Ca^{2+} concentration was more important than the lowest recorded fibrinogen concentration, acidosis and platelet count in predicting hospital mortality. Major risk factors for severe hypocalcaemia included acidosis and amount of FFP transfused.[498] Whole blood clotting time is prolonged in rats with severe ionised hypocalcaemia.[499]

FVIIa activity is calcium dependent. Thus, Ca^{2+} may stimulate intrinsic FVIIa activity by a combination of charge neutralisation and loop stabilisation.[500]

7.2.2 Emergency radiological/surgical interventions to reduce blood loss

7.2.2.1 Introduction

Angiotherapy can be diagnostically and therapeutically effective in patients with gastrointestinal bleeding. It provides a surgical alternative for patients with high surgical risk. Candidate patients have typically failed to respond to medical and/or endoscopic therapy.

Recommendations

We suggest that endovascular embolisation is a safe alternative to open surgical intervention after failed endoscopic treatment for upper gastrointestinal bleeding. **2C**

We suggest superselective embolisation as primary therapy for treatment of angiogram positive lower gastrointestinal bleeding. **2C**

We suggest embolisation as first-line therapy for arterial complications in pancreatitis. **2C**

Transcatheter arterial embolisation (TAE) is well tolerated and effective for upper gastrointestinal bleeding after failed endoscopic treatment.[501,502] It has a lower mortality rate than surgery,[503,504] and low incidences of technique-related complications and recurrent bleeding.[505,506] When a microcatheter cannot be advanced to the bleeding site, TAE with N-butyl cyanoacrylate may be used to treat upper gastrointestinal bleeding, even in coagulopathic patients.[507]

TAE can also be used for lower gastrointestinal bleeding,[508] with a success rate of 76–97% and low frequencies of acute ischaemia or recurrent bleeding.[509–511]

TAE is less invasive than surgery and equally successful in controlling arterial bleeding in pancreatitis.[512] In patients with head and neck cancer and massive tumour bleeding, TAE has a low incidence of adverse events and is associated with longer survival than that in patients who are not candidates for the procedure.[513]

7.3 Cost implications

7.3.1 Introduction

Hospital care providers have limited resources and funds allocated for transfusion divert funding from competing clinical and therapeutic strategies. The total cost of supplying patients with haemostatic therapies involves a complex array of activities surrounding the supply process, together with the cost of the consequences following administration. For example, unnecessary transfusions are likely to be associated with unnecessary morbidity and additional indirect hospitalisation costs. In this section, we assess the direct and indirect cost implications of haemostatic therapies.

7.3.2 Do bleeding, massive haemorrhage and transfusion of allogeneic blood products increase costs?

Recommendation

Bleeding and transfusion of allogeneic blood products independently increase morbidity, mortality, length of stay in ICU and hospital, and costs. **B**

Bleeding and transfusion of allogeneic blood products (e.g. packed RBCs, FFP, platelets) are independently associated with increased morbidity and mortality.[3,4,321,388,396,399,400,514–519] Thus, allogeneic blood transfusion is associated with increased costs.[515,520] These costs can be differentiated into primary or acquisition costs for allogeneic blood products (paid by the hospital or the government), activity based costs of blood transfusion (including all process costs from the indication to blood transfusion until monitoring of effects and adverse events) and secondary costs of transfusion-associated adverse events.[521] Acquisition costs for allogeneic blood products differ widely among countries in Europe and are difficult to determine in countries where hospitals do not have to pay for allogeneic blood products because these are supplied 'free of charge' by the government. However, activity based costs are usually 3.2–4.8 times higher than acquisition costs.[522] Some hospitals use virtual internal transfer prices, which have to be 'paid' by the transfusing department to the blood bank in order to compensate for activity based costs of the blood bank (e.g. storage and crossmatching). Furthermore, transfusion-associated adverse events such as acute lung injury (ALI), transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), nosocomial infections and sepsis, as well as ischaemic events (myocardial infarction, stroke, acute renal failure, multiple organ failure) are associated with secondary costs for hospitals, governments and health insurance companies. It has been shown that each additional day with mechanical ventilation at a US ICU increases the hospital cost by $3800–4000.[523,524] In the UK, the 'return-to-theatre cost' resulting from a bleeding complication in cardiac surgery has been calculated as £2617.[525] Furthermore, a study in cardiac surgery in Augsburg, Germany, demonstrated that excessive postoperative haemorrhage, defined as drainage volume >200 ml in any one of the first 6 h after surgery, was associated with significant increases in adverse events (e.g. four-fold increase in the incidence of stroke; incidence of renal failure doubled), length of ICU stay (doubled), mortality (four-fold increase) and hospital costs (increased from €8027 to €15 404).[526] Murphy *et al.*[515] reported that overall hospitalisation costs increased by >40% in transfused compared with non-transfused patients in cardiac surgery in the UK. Therefore, clinical interventions which prevent or address severe perioperative bleeding, reduce transfusion requirements and reduce transfusion-associated adverse events are likely to be cost-effective.

7.3.3 Does prophylactic use of antifibrinolytic drugs or recombinant factor VIIa reduce costs?

Recommendations

Lysine analogues (tranexamic acid and ε-aminocaproic acid; EACA) reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several settings of major surgery and trauma. **A**

We recommend restricting the use of rFVIIa to its licensed indication because, outside these indications, the effectiveness of rFVIIa to reduce transfusion requirements and mortality remains unproven and the risk of arterial thromboembolic events as well as costs are high. **1A**

Literature regarding the use of aprotinin to reduce bleeding and transfusion requirements has not been analysed because aprotinin was withdrawn from the market in 2007.[475,527,528]

Lysine analogues (tranexamic acid and EACA) have been shown to reduce the requirement for allogeneic blood transfusion in orthopaedic surgery,[477,529–538] trauma,[18,481]

cardiac surgery,[475,528,539–544] postpartum haemorrhage,[19,545,546] and liver resection and transplantation.[476,480,483,540,547,548]

Head-to-head comparisons show a lower risk of death with lysine analogues compared with aprotinin. The lysine analogues appear to be free of serious adverse effects, but safety data are sparse.[480] Tranexamic acid has been shown to be cost-effective, reducing transfusion requirements without increasing the incidence of deep vein thrombosis.[535] Lysine analogues appear to be particularly cost- and lifesaving in countries with limited financial resources.[549] Cost-effectiveness analysis based on the CRASH-2 trial data indicated that early administration of tranexamic acid to bleeding trauma patients is highly cost-effective in all income settings.[550]

No prospective randomised trials dealing with the prophylactic administration of rFVIIa have shown any effect on mortality.[467,540,551–554] The costs for 400 $\mu g\,kg^{-1}$ rFVIIa are very high compared to a reduction in transfusion requirement of 2.6 U RBCs. Prospective randomised trials in patients with intracerebral haemorrhage showed a significantly increased incidence of arterial thromboembolic complications, including myocardial and cerebral infarction (7 vs. 2% [$P = 0.12$] and 10 vs. 1% [$P = 0.01$], respectively).[555–557] A distinct trend towards serious thromboembolic adverse events, including stroke, was observed in prospective randomised studies in liver transplantation (placebo 10%; 60 $\mu g\,kg^{-1}$ rFVIIa 19%; 120 $\mu g\,kg^{-1}$ rFVIIa 12%; $P > 0.05$) and cardiac surgery (placebo 7%; 40 $\mu g\,kg^{-1}$ rFVIIa 14% [$P = 0.25$]; 80 $\mu g\,kg^{-1}$ rFVIIa 12% [$P = 0.43$]).[558,559] Most recent guidelines recommend not to use rFVIIa in non-approved indications. Its emergency use should be restricted to situations in which all other options failed to control severe bleeding.[540,560–563]

7.3.4 Does cell salvage reduce costs?

Recommendation

Cell salvage can be cost-effective. **A**

Cell salvage has been shown to be cost-effective in minimising perioperative transfusion of allogeneic blood products.[363,564,565]

7.3.5 Do formula driven transfusion protocols (1:1:1 concept for RBC:FFP:platelet transfusion) reduce costs?

Recommendation

The cost-effectiveness of a formula driven transfusion protocol has not been investigated.

Several retrospective and some prospective cohort studies – mostly performed in military trauma patients – suggest that early fresh frozen plasma transfusion with an FFP to PRBC ratio between 1:2 and 1:1 reduces 30-day mortality.[566–570] However, the evidence for this is of low quality, with a lack of prospective randomised trials.[15,16,571–573] There are no data on the impact of formula driven transfusion protocols on costs.

7.3.6 Does implementation of point-of-care diagnostics (thromboelastography, thromboelastometry, platelet function tests such as whole-blood impedance aggregometry) and subsequent goal-directed therapy reduce costs?

Recommendation

Implementation of transfusion and coagulation management algorithms (based on ROTEM/TEG) can reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. **B**

O'Keeffe *et al.*[574] and Cotton *et al.*[575] demonstrated in two retrospective studies in trauma patients that the implementation of a massive transfusion or exsanguination protocol significantly reduced overall blood product consumption and produced cost savings. Furthermore, Görlinger *et al.* showed in two retrospective studies in visceral surgery, liver transplantation and cardiovascular surgery that the implementation of a thromboelastometry-based transfusion and coagulation management algorithm significantly reduced transfusion requirements and costs.[120,576] These results were confirmed by a recent prospective randomised clinical trial in coagulopathic cardiac surgery patients.[119] A significant reduction in transfusion requirements, transfusion-associated adverse events and costs, as well as improved outcomes (including 6-month mortality), was demonstrated in the POC compared to the control group.

In principle, point-of-care tests of haemostatic function can facilitate the optimal management of excessive bleeding and reduce transfusion by enabling tailored haemostatic therapy and differentiation between microvascular and surgical bleeding. The potential reductions in allogeneic blood product transfusion and re-exploration rates have important implications for overall patient safety and healthcare costs. For example, re-exploration for bleeding in patients undergoing coronary artery bypass surgery is associated with a 4.5-fold increase in overall perioperative mortality.[185,526,577] Spalding *et al.*[578] (1422 cardiac surgery patients) and Görlinger *et al.*[120] (3865 cardiac surgery patients) demonstrated significant reductions in allogeneic blood product transfusion and cumulative costs for allogeneic blood products and coagulation factor concentrates after implementation of thromboelastometry-guided coagulation management algorithms. Similar results, including significant reductions in transfusion and coagulation management costs, were reported by Görlinger *et al.*,[120,576] Weber *et al.*[119] and Hanke *et al.*[579] after implementation of thromboelastometry-guided algorithms in visceral surgery, liver transplantation, and aortic arch replacement in acute type A aortic dissection in a German university hospital. Further multicentre prospective randomised clinical trials evaluating ROTEM/TEG-guided goal-directed

therapy ('theragnostic' approach) versus fixed ratio concepts (1:1:1 approach) in trauma patients and other clinical settings are urgently needed.

7.3.7 Does goal-directed therapy with coagulation factor concentrates (fibrinogen and/or prothrombin complex concentrate) reduce costs?

Recommendation

Goal-directed therapy with coagulation factor concentrates (fibrinogen and/or PCC) may reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. **B**

Fibrinogen deficiency plays a major role in trauma-induced coagulopathy and other clinical settings associated with severe bleeding.[414,425,436,562,580–582] Administration of fibrinogen concentrate has been demonstrated to be consistently effective in animal models and in patients with acquired fibrinogen deficiency.[420,422,426,581,583–585]

The efficacy, safety and cost-effectiveness of modern four-factor PCCs for rapid reversal of oral anticoagulation has been proven in several cohort and prospective, randomised studies.[449,563,586–598]

There is growing evidence that targeted therapy using coagulation factor concentrates guided by viscoelastic measurements enables effective correction of severe coagulopathy.[599–602] Görlinger *et al.*[120] demonstrated in a retrospective study (3865 cardiac surgery patients) that first-line therapy with coagulation factor concentrates (fibrinogen and PCC) based on point-of-care coagulation testing (ROTEM and Multiplate) decreased allogeneic blood transfusion, thrombotic/thromboembolic events and costs, and a more recent study confirmed these results.[119] Similar results, including significant reduction of transfusion and coagulation management related costs, were reported by Görlinger *et al.*[576] in visceral surgery and liver transplantation. Furthermore, in a study modelling the cost-effectiveness of PCC in emergency warfarin reversal in the United Kingdom, PCC appeared to be more cost-effective than FFP.[597]

7.3.8 Is the use of coagulation factor concentrates (fibrinogen and/or prothrombin complex concentrate) associated with an increased incidence of thromboembolic events and costs?

Recommendation

Thromboembolic events are associated with increased inhospital and post-hospital costs. **B**

Targeted therapy with fibrinogen and/or PCC guided by ROTEM/TEG is not associated with an increased incidence of thromboembolic events. **C**

Both bleeding and blood transfusion increase the incidence of ischaemic and thromboembolic adverse events and costs.[514] Here, both bleeding complications and thromboembolic events result in significantly increased costs both inhospital and after discharge.[603–605] Furthermore, off-label use of rFVIIa, either prophylactically or therapeutically, has been shown to be associated with an increased risk of arterial thromboembolic events.[554] However, Görlinger *et al.*[120] demonstrated in a large retrospective cohort study (3865 cardiac surgery patients) that first-line therapy with fibrinogen concentrate and PCC based on ROTEM analysis was associated not only with decreased allogeneic blood transfusion but also with a significantly reduced incidence of thrombotic/thromboembolic events (1.77 vs. 3.19%; $P = 0.0115$) and costs. These results were confirmed by a recent study in which the incidence of thromboembolic events was 0% in the POC versus 4% in the control group.[119] This suggests that secondary costs may be reduced by preventing thromboembolic events due to a targeted haemostatic therapy in bleeding patients. However, this effect has to be confirmed by larger safety studies. Furthermore, a recently published cohort study on the safety and efficacy of PCC and fibrinogen concentrates in 266 patients undergoing liver transplantation did not show a significantly increased incidence of thromboembolic events in patients receiving coagulation factor concentrates compared to patients who did not need any haemostatic intervention (7.1% vs. 4.5%; $P = 0.31$).[606] Details about the risk of thromboembolic events associated with PCC in the setting of VKA reversal are presented in section 7.3 and section 8.3.

8 MULTIMODAL APPROACH (ALGORITHMS) IN SPECIFIC CLINICAL FIELDS

8.1 Cardiovascular surgery

8.1.1 Introduction

Complex cardiovascular surgery may be accompanied by major blood loss, which can lead to loss and consumption of coagulation factors and haemodilution. Coagulopathy in cardiac surgery patients may be exacerbated by concurrent antithrombotic therapy, extracorporeal circulation, hypothermia and volume replacement using crystalloids/colloids.[607–610] Failure to restore haemostasis and restrict perioperative bleeding increases the risk of re-exploration, transfusion requirements, time spent in the ICU, morbidity and mortality.[611–613] In this section, we assess the best evidence on the use of different haemostatic therapies to control perioperative bleeding in cardiovascular surgery.

8.1.2 Which therapies influence perioperative bleeding when administered in the preoperative period?

Recommendations

Withdrawal of aspirin therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. **A**

Withdrawal of clopidogrel therapy increases the risk of thrombosis; continuation of clopidogrel therapy increases the risk of bleeding. **A**

We recommend that a prophylactic dose of low molecular weight heparin should be administered subcutaneously 8–12 h before elective CABG surgery. This intervention does not increase the risk of perioperative bleeding. **1B**

We recommend that tranexamic acid or EACA should be considered before CABG surgery. **1A**

We suggest considering prophylactic preoperative infusion of 2 g fibrinogen concentrate, because it may reduce bleeding following elective CABG surgery. **2C**

Prothrombin complex concentrate is effective for rapid reversal of oral anticoagulation before cardiac surgery. **A**

8.1.2.1 Antiplatelet therapies

Aspirin. Aspirin is widely used to treat coronary artery disease. Because aspirin impairs platelet aggregation, discontinuation of aspirin therapy may be considered before elective CABG surgery to minimise perioperative bleeding risk. Management of patients receiving aspirin has been discussed in several guidelines which recommend that aspirin is withdrawn between 2 and 10 days before elective CABG surgery.[364,614–616]

Urgent or emergency CABG is often performed on patients receiving aspirin up to the day of surgery. A recent meta-analysis of eight RCTs concluded that treatment with $\geq$325 mg per day of aspirin within 7 days of on-pump CABG surgery increased postoperative mediastinal drainage volume (doses <325 mg did not increase bleeding).[617] The authors concluded that a large RCT is needed to assess the effects of preoperative aspirin in the contemporary cardiovascular setting. These data corroborated findings from another meta-analysis (ten studies; five RCTs)[618] and a single-blind RCT ($n = 200$),[619] each showing that aspirin intake <7 days before CABG increased postoperative chest-tube drainage volume and RBC and FFP transfusion requirements. Among the studies included in the meta-analysis by Alghamdi *et al.* was a double-blind RCT demonstrating that the increased blood loss associated with preoperative aspirin was most apparent for patients carrying the GPIIIa allele PI^{A2}.[106] For these patients, additional haemostatic measures such as antifibrinolytic drugs, FFP or platelet transfusions may be considered.[106]

Clopidogrel. Preoperative clopidogrel therapy may increase postoperative bleeding after CABG. Existing guidelines recommend discontinuing clopidogrel 5–7 days before elective surgery.[614–616,620] A meta-analysis of 11 comparative studies (4002 patients) concluded that clopidogrel administration within 5–7 days before urgent CABG surgery increases blood loss and transfusion requirements for RBC, FFP and platelets.[621] These findings were supported by a later systematic review (23 studies) reporting that clopidogrel exposure within 7 days before CABG could increase major bleeding, haemorrhagic complications and transfusion requirements.[622] In elective CABG, a three-arm RCT ($n = 130$) subsequently compared clopidogrel therapy continued up to surgery with clopidogrel discontinuation at 3 or 5 days preoperatively.[623] Continued clopidogrel therapy resulted in increased blood loss at 12 h and at drain removal, plus increased postoperative homologous blood and FFP transfusion. Outcomes did not differ significantly between clopidogrel discontinuation at 3 vs. 5 days.

8.1.2.2 Heparin

Heparins may be administered before CABG to reduce the risk of deep vein thrombosis, particularly following discontinuation of antiplatelet therapy. In a prospective study ($n = 75$) comparing preoperative aspirin, subcutaneous unfractionated heparin (UFH) and a no-treatment control, preoperative UFH therapy caused the greatest reduction of postoperative chest-tube drainage volume following CABG surgery.[624] Recent guidelines from the American College of Cardiology Foundation and the American Heart Association[625] recommend that the use of UFH can be continued until a few hours before CABG and that low molecular weight heparin (LMWH) can be administered $\leq$12 h before surgery, each without increased perioperative blood loss. Prospective comparison ($n = 64$) of subcutaneous LMWH (enoxaparin), intravenous heparin and no-treatment control has shown that enoxaparin does not increase bleeding or transfusion requirements when given >8 h before coronary artery bypass.[626] Additionally, a randomised comparison ($n = 43$) of UFH and enoxaparin showed that subcutaneous administration of each, up to 12 h before surgery, has similar effects on coagulation parameters, whole blood count, and RBC and FFP transfusion requirements following elective CABG surgery.[627]

8.1.2.3 Warfarin

No studies addressing the effects of preoperative warfarin therapy on perioperative bleeding in cardiovascular surgery were retrieved. Recommendations concerning cessation of warfarin therapy before cardiac surgery have been presented elsewhere.[614]

8.1.2.4 Antifibrinolytic therapy (tranexamic acid and ε-aminocaproic acid)

Numerous studies have reported the use of the antifibrinolytic drugs aprotinin, tranexamic acid and EACA to reduce blood loss in cardiovascular surgery. However, aprotinin was withdrawn worldwide following a multicentre RCT ($n = 2331$) which demonstrated an increased risk of mortality associated with its use, compared with tranexamic acid and EACA, in high-risk cardiac surgery.[475] Recent Italian recommendations for preoperative management of perioperative transfusion report that

tranexamic acid is favoured over EACA in cardiovascular surgery due to the increased potency of tranexamic acid and the increased availability of supporting evidence.[47]

Tranexamic acid is typically administered continuously during surgery, although use of a single preoperative bolus has been reported. A best evidence topic presented 12 studies reporting prophylactic use of tranexamic acid in cardiac surgery and concluded that tranexamic acid reduces blood loss, transfusion requirements and reoperation due to bleeding.[628] Among the doses reported were single boluses in the ranges of 2–10 g and 20–150 mg kg^{-1} before sternotomy. One double-blind placebo-controlled randomised trial ($n = 80$) also showed that 30 mg kg^{-1} tranexamic acid given immediately before CPB reduced blood loss up to 16 h after elective CABG in patients receiving aspirin up until surgery.[539] Consistent with these data, a double-blind placebo-controlled randomised trial ($n = 100$) showed that 2 g tranexamic acid administered before incision reduced 4 h postoperative blood loss after off-pump CABG with cell salvage.[629] This confirmed results from two previous placebo-controlled randomised trials assessing the efficacy of 100 mg kg^{-1} tranexamic acid administered before incision. One double-blind trial ($n = 312$) reported tranexamic acid to reduce perioperative blood loss and transfusion rates during CABG with cardiopulmonary bypass (CPB);[630] the other ($n = 22$) demonstrated that tranexamic acid reduced intra- and postoperative blood loss during elective surgery with CPB.[631]

No prospective studies were identified which compared a single preoperative bolus of tranexamic acid with tranexamic acid administration throughout surgery. However, a four-arm prospective randomised trial ($n = 150$) compared a preoperative bolus of EACA with two intraoperative EACA dosing regimens and a no-treatment control in elective CABG.[632] Although EACA administration reduced postoperative chest-tube drainage volume when administered preoperatively, the effect was significantly enhanced by administering EACA intraoperatively.

8.1.2.5 Desmopressin (DDAVP)

No evidence was identified describing preoperative use of desmopressin in cardiovascular surgery. Existing guidelines on perioperative blood transfusion and blood conservation in cardiac surgery suggest preoperative utility of desmopressin may be limited to a small number of patients diagnosed as having defects in primary haemostasis.[364]

8.1.2.6 Allogeneic blood products (fresh frozen plasma, platelets and cryoprecipitate)

A prospective randomised trial ($n = 40$) was identified in which FFP was compared with prothrombin complex concentrate (PCC) for reversal of oral anticoagulation prior to CPB in semi-urgent cardiac surgery.[633] Patients receiving FFP did not reach target INR values within 15 min and even multiple FFP dosing failed to achieve the target INR in 80% of cases, necessitating administration of PCC. No further studies were identified which evaluated preoperative transfusion with FFP, platelets or cryoprecipitate.

8.1.2.7 Coagulation factor replacement therapy

Antithrombin (AT) concentrate. It has been proposed that AT (previously AT III) may limit consumptive coagulopathy by suppressing thrombin generation during cardiac surgery. This was investigated in a double-blind RCT ($n = 20$) in which placebo or AT was infused before incision in elective CABG patients.[634] No difference in postoperative blood loss at 6 or 12 h was evident between the AT and placebo groups. Recommendations on the use of AT concentrates suggest that further studies are needed in patients undergoing extracorporeal circulation.[635]

Fibrinogen concentrate. A prospective randomised pilot study ($n = 20$) demonstrated that prophylactic fibrinogen infusion is potentially useful for reducing bleeding after elective CABG.[430] Compared with untreated controls, patients receiving 2 g fibrinogen concentrate immediately before surgery experienced reduced 12 h chest-tube drainage volume, with no apparent hypercoagulability.

Prothrombin complex concentrate (PCC). A four-factor PCC has been shown to be more effective than FFP for reversal of oral anticoagulation in semi-urgent cardiac surgery.[633] Compared with FFP, administration of a half-dose of PCC (based on body weight and initial INR, according to the manufacturer's instructions) prior to CPB resulted in faster correction of INR, with less associated bleeding.

Recombinant activated factor VII (rFVIIa). rFVIIa has been administered preoperatively ahead of successful palliative open heart surgery in a cyanotic infant with FVII deficiency.[636] A dose of 30 μg kg^{-1} rFVIIa was administered 2 h before surgery and then another immediately before surgery, with further doses postoperatively. No further reports of preoperative rFVIIa therapy were identified.

8.1.3 Which therapies can be used to control bleeding intraoperatively?

Recommendations

We recommend that intraoperative tranexamic acid or EACA administration should be considered to reduce perioperative bleeding in high-, medium- and low-risk cardiovascular surgery. **1A**

We recommend that tranexamic acid should be applied topically to the chest cavity to reduce postoperative blood loss following CABG surgery. **1C**

We recommend that fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiovascular surgery. **1B**

We suggest that recombinant FVIIa may be considered for patients with intractable bleeding during cardiovascular surgery once conventional haemostatic options have been exhausted. **2B**

8.1.3.1 Heparin

Heparin anticoagulation is used during cardiovascular surgery to limit coagulation factor activation, thus preventing overt thrombosis of the CPB circuit. Heparin dosing may be partially influenced by the length of time spent on CPB and patient responses to heparin may be variable. Dosing and monitoring of heparin anticoagulation is addressed in guidelines on perioperative blood conservation management in cardiac surgery[364] and also on antiplatelet and anticoagulation management in cardiac surgery.[614] We retrieved four prospective studies ($n = 26$, $n = 39$, $n = 44$ and $n = 53$) investigating heparin monitoring using heparin concentration-based approaches, as opposed to a standard activated clotting time-based approach, during cardiac surgery.[637–640] Use of heparin concentration-based systems was consistently associated with reduced postoperative blood loss and increased avoidance of transfusion. Although useful in principle, heparin concentration-based monitoring is not widely used in clinical practice. In addition, a number of monitoring devices are available, so large randomised trials comparing different systems may be warranted.

8.1.3.2 Protamine

Administration of protamine is commonly used to reverse the effects of heparin anticoagulation. Correct dosing of protamine is important because insufficient protamine results in residual heparin. Conversely, excess protamine also impairs coagulation,[641] possibly due to antiplatelet activity.[642] Protamine dosing in cardiac surgery is addressed in guidelines on the management of perioperative blood conservation[364] and also on the management of antiplatelet and anticoagulation therapy.[614] The prospective studies that we identified which investigated heparin monitoring using heparin concentration-based approaches all found that heparin concentration-based measurements led to administration of smaller doses of protamine.[637–640] If these results are confirmed in larger studies, and if such approaches become part of normal practice, heparin concentration-based monitoring could improve the accuracy of protamine dosing. Another important issue concerning protamine administration in cardiac surgery is uncertainty over acceptable ratios of protamine to heparin. Typical ratios of protamine to heparin are around 1.3:1, although a best evidence topic on the risk of bleeding associated with high-dose protamine reported that increased bleeding and impaired platelet function had not been reported below a protamine to heparin ratio of 2.6:1.[643] This contrasts with reports suggesting that lower ratios (1.5:1 in *vitro*[642] and 1.3:1 *in vivo*[644]) can prolong coagulation and impair platelet function. Further studies are required to clarify the most appropriate ratios of protamine to heparin for use in cardiac surgery.

8.1.3.3 Antifibrinolytic therapy (tranexamic acid and ε-aminocaproic acid)

Intraoperative antifibrinolytic therapy is covered in guidelines for blood conservation[364] and anticoagulation management[614] in cardiac surgery. Each recommends using aprotinin, tranexamic acid or EACA to limit blood loss and transfusion requirements. Safety and efficacy outcomes for each drug have been compared in a meta-analysis of 138 RCTs in cardiac surgery.[528] Aprotinin, tranexamic acid and EACA all reduced perioperative blood loss and RBC transfusion compared with placebo. High-dose aprotinin showed the greatest efficacy, although aprotinin also increased the risk of renal dysfunction. This finding was consolidated by the BART (blood conservation using antifibrinolytics in a randomised trial) study ($n = 2331$),[475] which compared aprotinin, tranexamic acid and EACA in high-risk cardiac surgery (all administered as a preoperative bolus, followed by continuous intraoperative infusion), and was terminated early due to an elevated mortality rate associated with aprotinin. Aprotinin was subsequently withdrawn from the market and further meta-analyses using RCT data have confirmed the increased mortality risk associated with aprotinin in cardiac patients.[645,646]

Since aprotinin was withdrawn, it has not been established whether tranexamic acid or EACA is the better therapeutic option. Further analysis of the BART study data found no differences in safety or clinical effectiveness of tranexamic acid and EACA, although lower costs were reported for EACA.[647] Data supporting EACA administration was identified from a double-blind, placebo-controlled randomised trial ($n = 78$) in which EACA was found to be as effective as aprotinin for reducing blood loss during CABG surgery.[648] Conversely, a recent three-arm RCT ($n = 90$) comparing antifibrinolytic drugs in open heart surgery found that both aprotinin and tranexamic acid significantly reduced blood volumes in suction bottles and drainage tubes compared with EACA;[649] tranexamic acid also exhibited the least evidence of renal dysfunction. Although neither tranexamic acid nor EACA has been conclusively demonstrated as being superior in the cardiovascular setting, we identified more high quality evidence published since 2007 which supports use of tranexamic acid than was identified for EACA. This includes a double-blind, placebo-controlled randomised trial ($n = 222$) showing that tranexamic acid (preoperative bolus followed by infusion throughout CPB) decreased chest-tube drainage volume and

transfusion requirements following elective CABG.[650] Also identified was a double-blind RCT ($n = 220$) evaluating tranexamic acid versus aprotinin infusion throughout primary CABG or valve replacement surgery,[651] which showed no overall difference in blood loss or RBC transfusion between treatment groups. Similarly, a three-arm RCT ($n = 298$) comparing aprotinin, tranexamic acid and placebo in low- to medium-risk CPB patients[652] found that tranexamic acid significantly reduced blood loss and transfusion requirements compared with placebo, without increasing the incidence of serious adverse events. Additionally, a meta-analysis of 25 RCTs ($n = 5411$) and four matched observational studies ($n = 5977$)[653] was retrieved, which concluded that tranexamic acid has clear benefits in reducing blood loss, reoperation for bleeding and transfusion with allogeneic blood components compared with placebo.

Tranexamic acid administration regimens vary widely.[645] Our evidence base typically reported an initial bolus after induction of anaesthesia, followed by continuous infusion during CPB. Tranexamic acid may also be added to the bypass circuit, or another bolus administered before chest closure. One RCT was identified which directly assessed the benefits of tranexamic acid given intraoperatively; a double-blind trial examined 67 children with cyanotic congenital heart defects undergoing surgery with CPB.[654] All patients received 15 mg kg^{-1} tranexamic acid before incision, then either placebo or an identical dose of tranexamic acid at the end of CPB. Blood loss and transfusion requirements did not differ between the groups. Tranexamic acid may also be used topically. A double-blind RCT ($n = 38$) compared topical application of tranexamic acid (1 g in 100 ml saline) or placebo to the pericardial and mediastinal cavities before chest closure following CABG.[655] Tranexamic acid reduced postoperative chest-tube drainage volume and platelet transfusion requirements compared with placebo.

Variation in EACA administration regimens has also been reported. [645] Two RCTs were identified which compared EACA dosing regimens. In the first study, patients ($n = 150$) were randomised to receive no EACA, one 150 mg kg^{-1} preoperative bolus, one 150 mg kg^{-1} preoperative bolus plus 1 g h^{-1} infusion for 6 h, or three separate 150 mg kg^{-1} boluses before, during and after CPB.[632] The greatest reduction in blood loss and transfusion requirements was seen in the groups receiving EACA intraoperatively. Neither intraoperative regimen proved superior to the other. In a subsequent study, patients ($n = 90$) received either placebo, a 150 mg kg^{-1} EACA bolus followed by a 15 mg kg^{-1} h^{-1} infusion of EACA commencing before incision, or a 150 mg kg^{-1} bolus of EACA followed by a 15 mg kg^{-1} h^{-1} infusion of EACA commencing after heparinisation.[656] Both EACA regimens reduced chest-tube drainage volumes but the timing did not affect outcomes, suggesting that EACA administration is unnecessary before heparinisation.

Most of the evidence which we retrieved involved use of CPB (on-pump surgery). Off-pump CABG surgery is associated with less blood loss and transfusion than on-pump CABG. A systematic review of eight RCTs was performed to determine the utility of tranexamic acid in off-pump CABG.[657] Tranexamic acid reduced the risk of allogeneic blood component transfusion, but larger trials were deemed necessary to draw conclusions about blood loss and adverse events. We also identified a meta-analysis (17 trials) supporting the use of antifibrinolytic drugs in CABG patients receiving aspirin throughout the perioperative period.[543] Tranexamic acid and EACA all reduced chest-tube drainage volume and perioperative transfusion requirements without increasing the rate of adverse events.

8.1.3.4 Allogeneic blood products (fresh frozen plasma, platelets and cryoprecipitate)

Patients undergoing cardiovascular surgery are regularly transfused with FFP and/or platelet concentrate. Some patients may also receive cryoprecipitate, although this has been withdrawn in many countries due to safety concerns.[434] Intraoperative use of FFP, platelets and cryoprecipitate is addressed in a guideline on perioperative blood transfusion and blood conservation in cardiac surgery[364] and also in recent Italian recommendations for intraoperative management of perioperative bleeding.[112]

We retrieved no studies examining the haemostatic efficacy of platelet or cryoprecipitate transfusion on perioperative bleeding in cardiac patients, although three systematic reviews were identified which questioned the efficacy of FFP. One review assessed the effects of prophylactic FFP transfusion at the end of CPB in six RCTs; four were conducted in patients undergoing CABG surgery and two reported cardiac surgery with CPB.[408] It was concluded that routine FFP transfusion following CPB did not reduce subsequent blood loss. These findings are consistent with a recent systematic review of RCTs since 2004 which evaluates the clinical effectiveness of FFP.[658] Twenty-one studies were included and a meta-analysis of the largest subgroup (cardiac surgery) showed no significant reduction in 24-h blood loss following FFP transfusion. In addition, a review of seventy studies (including 21 set in cardiovascular surgery) concluded that FFP transfusion was not clinically effective and may even be detrimental.[585] In each systematic review, the evidence was reported to be of low quality due to small patient numbers and/or poor methodology.

8.1.3.5 Desmopressin (DDAVP)

Much of the evidence concerning intraoperative use of desmopressin has been considered in an existing guideline on perioperative transfusion and blood conservation in cardiac surgery.[364] Potential use of desmopressin is suggested to be limited to excessively bleeding patients

with primary haemostasis disorders, such as CPB-induced platelet dysfunction and type 1 VWD. Consistent with this, we retrieved two RCTs reporting that administration of 0.3 $\mu g\,kg^{-1}$ desmopressin at the end of CPB did not reduce perioperative blood loss or transfusion requirements in elective CABG ($n = 66$)[659] or complex congenital heart surgery ($n = 60$).[660] Similar findings were reported following desmopressin treatment of 100 CABG patients receiving aspirin until the day before surgery.[485]

8.1.3.6 Coagulation factor replacement therapy

Factor XIII concentrate. A three-arm, double-blind RCT ($n = 75$) was identified which investigated FXIII concentrate as haemostatic therapy in coronary surgery with extracorporeal circulation.[443] Following protamine administration, patients received placebo or 1250 or 2500 U of FXIII. No significant differences in postoperative blood loss or transfusions were observed. Subgroup analysis indicated that FXIII therapy may be most effective in patients displaying subnormal FXIII levels following CPB.

Fibrinogen concentrate. Two systematic reviews have suggested fibrinogen concentrate to be potentially useful for treating surgical bleeding.[585,661] One review included 21 trials investigating efficacy of fibrinogen concentrate; three were prospective studies reporting intraoperative use in cardiovascular surgery.[585] The second review included four reports; two were prospective studies in cardiovascular surgery.[661] Each review concluded that fibrinogen concentrate therapy could improve clot firmness and decrease transfusion requirements, blood loss and postoperative drainage volumes. The evidence was acknowledged to be of insufficient quality, indicating a need for large RCTs.

Since then, data has become available from a randomised, double-blind, placebo-controlled trial ($n = 61$)[662] which supports intraoperative infusion of fibrinogen concentrate during complex cardiovascular surgery. Patients with diffuse bleeding following CPB were treated with thromboelastometry-guided fibrinogen concentrate as first-line haemostatic therapy, which reduced the need for transfusion with RBC, FFP and platelets.[662] These data corroborated findings from two smaller prospective cohort studies, one in repair of thoracoabdominal aortic aneurysm ($n = 18$),[117] the other involving aortic valve operation with ascending aorta replacement ($n = 15$).[116] Similarly, thrombelastography guided fibrinogen concentrate therapy following CPB has been reported to reduce postoperative chest tube drainage volume and FFP transfusion in cyanotic children undergoing cardiac surgery.[663]

Prothrombin complex concentrate. Recommendations on the use of PCC suggest that it may help to control intractable bleeding in major surgery,[635] although there is little evidence so far to support this indication in cardiovascular surgery. Two retrospective reports were identified describing intraoperative PCC administration in cardiac patients. Analysis of five patients undergoing CABG and two patients undergoing valve replacement suggested that PCC could be valuable for controlling bleeding in patients responding poorly to standard blood products.[457] An earlier chart review of cardiothoracic surgical patients ($n = 60$) indicated that PCC could safely reduce blood product consumption.[664] Larger, prospective evaluations are required.

Recombinant activated factor VII. Although indicated for patients with congenital coagulation factor deficiencies, use of rFVIIa has been frequently reported for unlicensed indications in patients with major bleeding.[665] Guidelines for the use of rFVIIa in massive bleeding[562] and for perioperative blood conservation in cardiac surgery[364] recommend that rFVIIa may promote haemostasis during severe intractable bleeding following CPB. However, due to concerns over potential thromboembolic risks, use of rFVIIa is recommended only if all conventional haemostatic options have been exhausted. Additionally, the patient's next of kin should be informed that rFVIIa is being used outside of the currently approved indications.[562]

We retrieved reports published subsequent to these guidelines which support existing recommendations for rFVIIa in cardiac surgery. Systematic reviews of rFVIIa in cardiac surgery (one including 35 studies and one including 46 studies),[666,667] paediatric cardiac surgery (29 studies)[668] and vascular surgery (15 studies)[669] concluded that rFVIIa may reduce severe haemorrhage but that large prospective randomised trials are required to define efficacy, dose and side-effects. Similarly, a systematic analysis of rFVIIa in on-pump cardiac surgery (19 studies) recommended against routine prophylaxis and emphasised that although rFVIIa may be considered as rescue therapy, high quality data supporting this indication is lacking.[670]

8.1.3.7 Fibrin sealant (fibrin glue)

Fibrin sealant consists of fibrinogen, thrombin and other additives and can be applied to wounds to create a fibrin-based clot and promote haemostasis. We retrieved a recent prospective RCT in which 82 senior patients received either fibrin sealant or bone wax injected into the sternal marrow cavity after CABG surgery involving CPB.[671] The fibrin sealant group displayed reduced postoperative chest-tube drainage volume, less RBC transfusion requirements and a shorter hospital stay. No differences in adverse outcomes were reported. Blinding was not reported so further trials may be required to confirm these findings.

8.1.4 Which therapies influence bleeding in the postoperative period?

Recommendations

We suggest that antiplatelet therapy with aspirin or clopidogrel may be administered in the early

postoperative period without increasing the risk of postoperative bleeding. **2C**

We suggest that rFVIIa may be considered for patients with intractable bleeding after cardiovascular surgery once conventional haemostatic options have been exhausted. **2B**

8.1.4.1 Antiplatelet therapies (aspirin and clopidogrel)

Guidelines on the use of aspirin and other antiplatelet agents during CABG surgery[616] and on antiplatelet and anticoagulation management in cardiac surgery[614] make several recommendations on the postoperative administration of antiplatelet therapies. We retrieved no further high quality evidence evaluating the effects of postoperative antiplatelet therapy on postoperative bleeding. However, a prospective, multicentre, observational trial was identified in which patients ($n = 5065$) undergoing CABG received aspirin therapy in the early postoperative period.[672] Aspirin was associated with numerous clinical benefits and was reported to have no association with increased postoperative bleeding. Another prospective observational trial investigated patients ($n = 117$) undergoing elective CABG (on- and off-pump) who were administered aspirin or aspirin plus clopidogrel in the early postoperative period, according to a predefined protocol.[673] Chest-tube drainage, transfusion frequency, transfusion quantity and risk of reoperation for bleeding were all comparable between the groups, indicating that early postoperative clopidogrel does not increase bleeding risks compared with aspirin alone.

8.1.4.2 Antifibrinolytic therapy (tranexamic acid and ε-aminocaproic acid)

A randomised, double-blind, placebo-controlled study was identified which investigated the effects of continued tranexamic acid dosing in the postoperative period following elective cardiac surgery involving CPB.[674] All patients ($n = 510$) received 1 g tranexamic acid before incision, a continuous infusion of 400 mg h^{-1} until the completion of operation, and 500 mg in the CPB prime. Thereafter, patients received an infusion for 12 h with placebo, 1 mg kg^{-1} h^{-1} tranexamic acid or 2 mg kg^{-1} h^{-1} tranexamic acid. Postoperative administration of tranexamic acid had no effect on blood loss or transfusion requirements.

8.1.4.3 Allogeneic blood products (fresh frozen plasma, platelets and cryoprecipitate)

No high quality evidence was identified supporting the efficacy of FFP, platelets or cryoprecipitate administered postoperatively following cardiovascular surgery. Administration of allogeneic blood components has been addressed recently by Italian recommendations for postoperative management of perioperative transfusion.[675]

8.1.4.4 Desmopressin (DDAVP)

No high quality evidence was identified supporting the efficacy of postoperative administration of desmopressin in cardiovascular surgery.

8.1.4.5 Coagulation factor replacement therapy

Recombinant activated factor VII. As described for intraoperative therapy, use of rFVIIa to control intractable bleeding constitutes an unlicensed indication. Due to the potential thromboembolic risks, rFVIIa should therefore be considered only if conventional haemostatic approaches have failed. In this situation, guidelines for the use of rFVIIa in massive bleeding[562] and for perioperative blood conservation in cardiac surgery[364] suggest that rFVIIa may be used for refractory bleeding following CPB. The patient's next of kin should be informed that rFVIIa is being used off-label.[562]

A best evidence topic was identified addressing the question: is rFVIIa useful for intractable bleeding after cardiac surgery?[676] Of 129 reports identified, 13 were presented as the best evidence. The study concluded that a dose of 60–90 μg kg^{-1} rFVIIa could be used for patients with intractable bleeding post-cardiac surgery, with a repeated dose after 2–4 h. A double-blind RCT ($n = 172$) was also identified in which rFVIIa was used to treat patients experiencing intractable bleeding after cardiac surgery.[559] Patients received placebo, 40 μg kg^{-1} 1 rFVIIa or 80 μg kg^{-1} rFVIIa, on average 2.8 h after admission to the postoperative care unit. Treatment with rFVIIa significantly reduced the incidence of reoperation for bleeding and subsequent transfusion requirements, although both rFVIIa groups exhibited a non-significant trend towards increased serious adverse events. This suggests the need for large RCTs to assess safety of rFVIIa in this setting.

8.1.5 What is the evidence for the use of haemostatic management algorithms in cardiovascular surgery?

Recommendations

We recommend the use of standardised haemostatic algorithms with predefined intervention triggers. **1A**

Several studies have demonstrated that standardised transfusion algorithms for administration of haemostatic therapy can result in reduced perioperative blood loss and transfusion requirements. A recent review evaluated eight studies (five prospective) using preset therapeutic transfusion triggers, measured using laboratory-based haemostasis tests and/or point-of-care coagulation monitoring devices, to guide haemostatic intervention during cardiovascular surgery. In seven of the eight studies, the use of an algorithm significantly reduced patient exposure to allogeneic blood products.[144]

We retrieved additional prospective studies which evaluated the effectiveness of standardised treatment algorithms in cardiovascular surgery. One RCT compared

cardiac surgery patients ($n = 69$) in whom perioperative transfusion management was conducted in accordance with either a strict TEG-guided protocol (using kaolin-activated TEG and PlateletMapping assays), or physician-directed administration with reference to aPTT, INR, fibrinogen concentration and platelet count.[677] TEG-based management reduced total blood product usage by almost 60% compared with the laboratory test-based approach, although this was not statistically significant. A larger RCT confirmed the potential value of TEG in guiding haemostatic management.[121] In this study, patients ($n = 224$) undergoing elective CABG with CPB again received transfusions based on either kaolin-activated TEG or clinicians' judgement combined with laboratory test results. Patients in the TEG group received significantly lower amounts of FFP, platelets and tranexamic acid, while the total number of units transfused was also lower compared with patients managed using laboratory tests and clinical judgement. Another RCT was identified which supports the use of viscoelastic point-of-care tests to guide coagulation management.[129] Patients ($n = 56$) requiring aortic surgery with hypothermic circulatory arrest were administered haemostatic interventions according to a ROTEM-guided transfusion algorithm (INTEM, HEPTEM, FIBTEM and APTEM tests) or based on 'standard practice' (transfusion guided by clinical judgement and laboratory test results). Postoperative blood loss and rate of reoperation for bleeding were comparable between groups, although ROTEM-guided therapy substantially reduced allogeneic transfusion requirements, particularly for FFP. Furthermore, recent studies have demonstrated that first-line therapy with coagulation factor concentrates (fibrinogen and PCC) based on point-of-care coagulation testing (ROTEM and Multiplate) decreases allogeneic blood transfusion, thrombotic/thromboembolic events and costs.[119,120]

8.2 Gynaecology and obstetrics

8.2.1 Gynaecological (non-pregnant) bleeding

8.2.1.1 Treatment of perioperative anaemia

Gynaecological operations such as cancer surgery and hysterectomy may be complicated by anaemia and perioperative blood loss.[678] Among gynaecological operations, excision of a malignant ovarian tumour is the most common cause of severe bleeding,[679] and transfusion and reoperation due to bleeding are prevalent in hysterectomy.[680,681]

Minimising gynaecological RBC transfusion

Recommendation

We suggest against normovolaemic haemodilution because it does not reduce allogeneic transfusion. **2A**

Gynaecological oncologists report a mean pre-chemotherapy transfusion threshold of 7.9 g dl^{-1} haemoglobin (higher for ovarian debulking; lower for endometriosis).[682] No evidence was identified comparing gynaecological RBC transfusion triggers with those in other settings.

Autologous transfusion[683–692] and intraoperative haemodilution[693–695] exemplify strategies to minimise allogeneic transfusion.[696] However, autotransfusion is associated with high costs, together with risks of laboratory and clerical errors.[696–698] In addition, transfusion of colloids can result in haemodilution, which may compromise coagulation[413,431] and therefore may not reduce allogeneic transfusions [699,700].

Should cell salvage be used in gynaecological surgery?

Recommendation

Cell salvage may reduce allogeneic transfusion in gynaecological (including oncological) surgery. **C**

Increasing evidence supports the use of filters to clear shed blood of cancer cells, avoiding reinfusion and dissemination.[701] Retrospective studies suggest that cell salvage reduces allogeneic transfusion requirements.[702–706]

Should intravenous iron or erythropoietin be used to correct perioperative anaemia?

Recommendations

We suggest using preoperative intravenous iron to reduce allogeneic transfusion requirements in gynaecological cancer patients receiving chemotherapy. **2B**

We suggest using intravenous iron to correct preoperative anaemia in women with menorrhagia. **2B**

Intravenous iron increases haemoglobin concentration and reduces RBC transfusion in anaemic gynaecological cancer patients receiving chemotherapy,[707,708] without compromising quality of life.[708] Intravenous iron corrects preoperative anaemia in patients with menorrhagia.[213] Preoperative erythropoietin increases haemoglobin concentration, particularly if co-administered with iron,[235,250,707,709,710] but concerns exist regarding safety in cancer patients.[678]

8.2.1.2 Coagulation monitoring and treatment

Gynaecological cancer patients are prone to increased blood viscosity and fibrinogen concentrations,[711–713] and perioperative transfusion >2 l increases the risk of postoperative venous thromboembolism.[713] Perioperative haemostatic monitoring and intervention is critical.

Use of standard laboratory tests and point-of-care devices for gynaecological coagulation monitoring

Recommendation

Preoperative fibrinogen and D-dimer evaluation in gynaecological cancer patients provide little useful information. **C**

Elevated preoperative plasma fibrinogen concentrations and positive D-dimer tests provide little clinically useful information.[714] PT, aPTT and INR may be elevated for several days postoperatively.[715]

What are the indications for fresh frozen plasma, platelets and fibrinogen replacement therapy?

Recommendation

Postoperative FFP transfusion is associated with an increased risk of venous thromboembolism in malignant gynaecological surgery. **C**

FFP transfusion after surgical exploration for resection of adnexal/peritoneal cancer appears to increase risk of venous thromboembolism without affecting survival,[715] although the study was prone to confounding-by indication bias. No relevant studies were identified for fibrinogen concentrate or cryoprecipitate in gynaecological surgery.

What are the indications for recombinant activated factor VIIa?

Recommendation

rFVIIa increases thromboembolic risk and has not been shown to reduce mortality. **B**

rFVIIa has been successfully administered for perioperative bleeding in malignant and non-malignant gynaecological surgery.[716] However, rFVIIa increases the risk of venous thromboembolism, without improving mortality.[717] No studies examining the use of PCC or FXIII were identified.

What are the indications for antifibrinolytics (tranexamic acid)?

Recommendations

Tranexamic acid reduces the frequency of late bleeding after cone biopsy of the cervix. **B**

Tranexamic acid reduces perioperative bleeding in gynaecological cancer surgery. **C**

We suggest against the use of tranexamic acid in benign gynaecological operations such as myomectomy. **2B**

Tranexamic acid reduces menstrual bleeding in menorrhagia without increased thrombotic risk.[718] Tranexamic acid also protects against late bleeding after cone biopsy of the cervix[719] and reduces blood loss in gynaecological cancer surgery[720], but not during myomectomy.[721]

8.2.2 Obstetric bleeding

8.2.2.1 Treatment of postpartum anaemia

Anaemia develops in up to 29% of third trimester pregnancies,[722] while postpartum bleeding is the major risk factor for severe postpartum anaemia.[723] Transfusion in this setting may complicate delivery.[414,724–728] Here, we assess whether treating obstetric haemorrhage requires correction of anaemia, and the therapeutic options available.

Related topics of PPH such as diagnosis of PPH, treatment of atony and retained placental tissue, arterial embolisation, etc. is beyond the scope of this guideline. We recommend other evidence-based clinical guidelines such as the WHO guidelines for the management of postpartum haemorrhage and retained placenta.[729]

Obstetric triggers for red blood cell transfusion

Recommendations

We recommend that peripartum haemorrhage should be managed by a multidisciplinary team. An escalating management protocol including uterotonic drugs, surgical and/or endovascular interventions, and procoagulant drugs should be available. **1C**

Risk awareness and early recognition of severe haemorrhage are essential. **C**

We suggest that patients with known placenta accreta are treated by multidisciplinary care teams. **2C**

Postpartum haemorrhage (PPH) should be treated promptly. Delayed recognition of and response to acute bleeding is a leading cause of maternal mortality and 'near misses'.[730] Suboptimal haematocrit during the acute phase of PPH is associated with end organ dysfunction.[731] In postpartum haemorrhagic shock, myocardial ischaemia is typically associated with impaired contractility at systolic blood pressure <88 mmHg, diastolic blood pressure <50 mmHg and heart rate >115 beats per min.[732,733]

No clinical studies of transfusion triggers in life-threatening obstetric haemorrhage were retrieved; however, general adherence to a haemoglobin threshold of 8.1 g dl^{-1} has been reported.[734]

There is currently debate over RBC transfusion triggers for postoperative anaemia.[735] Up to 68% of postpartum transfusions may not adhere to guideline recommendations,[734,736–738] and RBC units are often transfused in duplicate without an obvious rationale. [735] Transfusion of 1–2 U of RBCs during postpartum recovery may not impact on length of hospital stay.[739]

Anaemia peaks at around 48 h after delivery but may initially go undetected.[736] Haemoglobin concentration and health related quality of life physical fatigue scores correlate in the first week postpartum.[740]

Early diagnosis and treatment of coagulopathic amniotic fluid embolism is associated with increased survival.[741] Treatment by a multidisciplinary team may reduce early maternal morbidity in women with placenta accreta, compared with standard obstetric care.[742]

Should cell salvage be used in obstetrics?

Recommendations

Cell salvage is well tolerated in obstetric settings, provided that precautions are taken against rhesus isoimmunisation. **C**

We suggest that using perioperative cell salvage during caesarean section may decrease postoperative homologous transfusion and reduce hospital stay. **2B**

Perioperative cell salvage has been used in obstetric surgery but is not widely established due to staff training and technology issues.[743] Concerns exist regarding potential amniotic fluid embolism and rhesus isoimmunisation.[744] Filters reduce contamination with amniotic fluid,[745–748] although fetal RBC may remain after leukocyte filtration;[747] therefore, Kleihauer testing and Anti-D treatment may be recommended.[749] Severe hypertension is rare following infusion of salvaged blood.[750]

Cell salvage may be useful for caesarean section, especially for Jehovah's Witnesses and when complicated by placenta praevia, placenta accreta or reoperation due to bleeding [744,750–755]. Jehovah's Witnesses who are prepared to accept perioperative cell salvage often require that the system be set up to allow for continuous connectivity, including during transport to the postoperative ward. A comparison with standard treatment has shown cell salvage to reduce postoperative homologous transfusion and hospitalisation.[756]

Intravenous iron or erythropoetin in the treatment of postpartum anaemia

Recommendations

We recommend that moderate (<9.5 g dl^{-1}) to severe (<8.5 g dl^{-1}) postpartum anaemia be treated with intravenous iron rather than oral therapy. **1B**

Intravenous iron supplementation improves fatigue at 4, 8 and 12 weeks postpartum. **B**

Insufficient evidence exists to support the transfusion-sparing effect of intravenous iron supplementation.

We suggest that treatment with erythropoietin may correct anaemia more rapidly than treatment with folic acid and iron. **2C**

Alternatives to RBC transfusion for maintaining haemoglobin concentrations are required. Patients with moderate (Hb < 9.5 g dl^{-1}) to severe (Hb < 8.5 g dl^{-1}) anaemia may benefit from intravenous iron therapy,[757–763] which elicits more rapid recovery from shorter treatment compared with oral therapy.[758–763] Intravenous iron may also improve fatigue score, but not overall quality life assessment, up to 12 weeks postpartum.[763] No evidence was identified comparing different intravenous iron therapies, and the safety of iron carboxymaltose requires further investigation.[764] In addition, the transfusion-sparing potential of intravenous iron remains unclear.[209]

Co-administration of erythropoietin and iron has been advocated for treating postpartum anaemia.[765,766] Treatment should begin within 96 h and appears to be safe.[767] Increased haemoglobin concentration has been reported following treatment of anaemic (Hb < 10 g dl^{-1}) parturients with erythropoietin and oral or intravenous iron,[767] although this evidence is from a small patient population. Erythropoietin and iron may be used to treat patients with severe anaemia (Hb < 8 g dl^{-1}) and pronounced clinical symptoms or rejection of donor blood.[757]

8.2.2.2 Postpartum haemorrhage: coagulation monitoring and management

Acquired obstetric coagulopathy affects approximately 21% of deliveries, with complications including PPH requiring transfusion,[725] increased risk of placental abruption,[768] placenta praevia and accreta,[769] amniotic fluid embolism,[741,770] retained dead fetus[771] and post-haemorrhagic shock.[772,773] Obstetric conditions also account for 1–5% of clinical cases of DIC.[774] In this section, we evaluate the evidence for coagulation monitoring in severe obstetric bleeding.

Fibrinogen measurement

Recommendations

We suggest assessing fibrinogen concentration in parturients with bleeding, as concentrations <2 g l^{-1} may identify those at risk of severe PPH. **2C**

Plasma fibrinogen concentrations increase during pregnancy to a normal third-trimester range of 4.5–5.8 g l^{-1}.[775] Fibrinogen concentrations decrease with increasing blood loss and may serve as a marker of haemostatic impairment.[87,776,777] Plasma fibrinogen concentration below 2 g l^{-1} is associated with the development of severe PPH, comprising a decrease in haemoglobin by ≥4 g dl^{-1}, transfusion of ≥4 U RBCs, requirement for haemostatic intervention (angiographic embolisation, surgical arterial ligation or hysterectomy) and death.[414] Evaluation of fibrinogen concentration at the onset of labour is of less predictive value.[778]

Platelet count

Recommendation

Platelet count <100 x 10^9 l^{-1} at the onset of labour, particularly combined with plasma fibrinogen concentration <2.9 g l^{-1}, may indicate an increased risk of PPH. **C**

Platelet count $<100 \times 10^9$ l^{-1} at the onset of labour is associated with increased risk of PPH and is exacerbated by plasma fibrinogen concentration <2.9 g l^{-1}.[778] Platelet count during the ninth month of pregnancy does not correlate with platelet count at the onset of labour.[778]

A single platelet count does not predict development of severe PPH. However, severe PPH typically involves a time-dependent decrease in platelet count, whereas non-severe PPH usually involves a stabilisation of platelet count during the first 24 h of bleeding.[414] Low platelet count is associated with increased RBC and FFP transfusion.[87]

Activated partial thromboplastin time and prothrombin time

Recommendation

aPTT and PT are of little predictive value for PPH. **C**

aPTT and PT are poor predictors of severe PPH.[414] aPTT, but not PT, shows a small but significant correlation with estimated blood loss in PPH, while increased PT and aPTT are associated with greater RBC and FFP transfusion requirements.[87]

Thrombelastography or thromboelastometry

Recommendation

Thromboelastometry can identify obstetric coagulopathy and hyperfibrinolysis and guide haemostatic therapy. **C**

FIBTEM, a bedside thromboelastometric fibrin clot quality test, provides results in 5–15 min and can indicate a reduced contribution of fibrinogen to clot strength.[779] FIBTEM maximum clot firmness is significantly decreased during PPH.

Thromboelastometric measurements can identify the hypercoagulability seen in normal pregnancy[775] and also in caesarean section,[780,781] pre-eclampsia and HELLP syndrome.[782] They can potentially allow rapid recognition of hyperfibrinolysis and guide therapy with tranexamic acid, fibrinogen concentrate, PCC, FFP and platelets.[770]

Hyperfibrinolysis

Overall fibrinolytic capacity decreases during pregnancy,[783,784] although there is little evidence of hyperfibrinolysis in severe PPH versus non-severe PPH.[414] Hyperfibrinolysis is associated with obstetric coagulopathic complications including shock, DIC and amniotic fluid embolism.[770]

8.2.2.3 Haemostatic treatment of obstetric haemorrhage

During normal pregnancy, maternal haematological adaptation includes anaemia, neutrophilia, mild thrombocytopaenia, increased levels of procoagulant factors and diminished fibrinolysis.[722] Here, we assess the specific perioperative transfusion requirements of obstetric patients due to pregnancy related haematological changes.

What are the indications for transfusion with fresh frozen plasma and platelets?

Recommendation

In life-threatening PPH, we suggest a transfusion protocol with a fixed product ratio or individualised procoagulant intervention and factor substitution. **2C**

A single centre US study reported that 0.87% of US deliveries involve transfusion with haemostatic blood products.[727] Approximately 1.25 in 1000 deliveries are complicated by major obstetric haemorrhage (requirement of >5 U RBCs).[731] RBC transfusion is accompanied by FFP and platelet transfusions in 20% and 16% of cases, respectively. [736] Transfusion of FFP, platelets and cryoprecipitate may be a marker for bleeding severity and volume of RBCs required.[731] An algorithm for managing obstetric haemorrhage[785] suggests transfusion with FFP if INR is >1.5, with platelets if the platelet count is $<25\ 000\,\mu l^{-1}$, and with cryoprecipitate if fibrinogen concentration is $<100\,mg\,dl^{-1}$. For uncontrolled, life-threatening haemorrhage, a multitransfusion protocol is recommended: 6 U RBCs, 4 U FFP and 1 U platelets.[785] Others advocate ROTEM-based assessment[770] or damage control resuscitation (RBC:FFP:platelet ratio of 1:1:1) for management of placenta accreta requiring multiple transfusions.[786]

Rapid haemostatic surgery avoiding hypothermia and using intravenous saline may enhance survival in a low-resource setting, based on data showing that 88% of Jehovah's Witnesses survived haemorrhagic shock following uterine rupture.[787]

What are the indications for fibrinogen substitution with fibrinogen concentrate or cryoprecipitate?

Recommendation

Considering physiologically elevated fibrinogen concentrations in pregnancy, we suggest that a higher trigger value for treating hypofibrinogenaemia may be required. **C**

Fibrinogen concentrations are typically elevated (approximately $5\,g\,l^{-1}$) in pregnancy[775], so the potential for FFP (which has an average fibrinogen concentration of $2.5\,g\,l^{-1}$)[581] to supplement fibrinogen concentration is limited. Fibrinogen concentrate represents an alternative therapy, and empirical use in bleeding patients (8–33% obstetric) has indicated potential reductions in blood loss and transfusion requirements.[426,583,584] Trigger levels for fibrinogen substitution vary between 1 and $2\,g\,l^{-1}$, with a mean administered dose of 2–4 g.[426,583,584,726,788] Studies investigating cryoprecipitate in obstetric patients were not identified.

No serious adverse events were reported with fibrinogen concentrate in the obstetric setting, although one study associated haemostatic treatment (including fibrinogen substitution) with an increased risk of venous thrombosis.[726]

What are the indications for the use of antifibrinolytic therapies (tranexamic acid) in obstetrics?

Recommendations

We recommend the administration of tranexamic acid in obstetric bleeding to reduce blood loss, bleeding duration and the number of units transfused. **1B**

We suggest that tranexamic acid be considered before caesarean section. **2C**

In antepartum bleeding, we suggest administration of tranexamic acid. **2B**

To balance the procoagulant effects which occur naturally during delivery, fibrinolysis is also increased.[783] However, abnormal fibrinolysis is associated with complications including placental abruption with antepartum bleeding,[722,789] intrauterine death[771] and amniotic fluid embolism.[722,741,790]

Antifibrinolytic therapy, used prophylactically for vaginal or caesarean delivery, or when postpartum bleeding evolves,[791] may prevent such complications. Several studies suggest that tranexamic acid administered 10–20 min before caesarean section may reduce perioperative blood loss.[546,791–794] Tranexamic acid may reduce antepartum bleeding in placental abruption and placenta praevia, and appears safe during pregnancy and postpartum.[791]

In a recent study, tranexamic acid reduced blood loss and 42-day transfusion requirements in PPH.[19] No severe side-effects (e.g. thromboembolic complications) were observed, although the study was not powered to assess safety. Mild transient adverse manifestations such as nausea, vomiting, dizziness and 'seeing stars' occurred more frequently in the tranexamic acid group than in the control group, possibly due to the relatively high dose used in this trial (4 g).

What are the indications for other coagulation factor concentrates (prothrombin complex concentrate and factor XIII)?

In a case of amniotic fluid embolism following vaginal delivery, stable clotting was achieved by thromboelastometry-guided coagulation therapy comprising tranexamic acid, fibrinogen concentrate, platelets and PCC, as well as RBC and FFP in a 1:1 ratio.[770] No further reports were retrieved describing PCC or FXIII therapy in obstetric patients with non-inherited coagulation deficiency.

What are the indications for the use of recombinant factor VIIa?

Recommendations

We recommend that rFVIIa should only be considered as last-line therapy because of its thromboembolic risk. **1B**

We suggest that fibrinogen concentration and number of platelets should be optimised before administration of rFVIIa. **2C**

rFVIIa can be considered as second-line haemostatic therapy alongside intrauterine tamponade, uterine compression sutures, pelvic vessel ligation and interventional radiology.[795] Case reports[796–821] and retrospective studies[795,822–824] support off-label use of rFVIIa for severe obstetric coagulopathic bleeding. Subjective evaluation has shown rFVIIa administration to arrest bleeding in 75–97% of cases.[466,824–827] rFVIIa may also prevent postpartum hysterectomy,[827] although other studies do not support this finding.[810,828] Administration of rFVIIa may not decrease transfusion requirements, although this may reflect its frequent use in complex coagulopathic bleeding.[828] Plasma fibrinogen concentration and platelet count should be optimised before administration of rFVIIa.[829]

Administration of rFVIIa was potentially linked to three thromboembolic events in a study including 110 otherwise healthy obstetric patients,[466] and its use in PPH has been associated with lower limb ischaemia and pulmonary embolism, albeit with favourable clinical outcomes.[830] Although rFVIIa potentially carries a thromboembolic risk, no difference in mortality has been identified in other patient categories.[717]

8.3 Orthopaedic surgery and neurosurgery

8.3.1 Bleeding risk of different orthopaedic and neurosurgical procedures

Recommendation

In elective orthopaedic surgery, we recommend the implementation of a blood transfusion protocol (algorithm), together with staff education. **1B**

There is a lack of standardised definitions for the reporting of bleeding events.[536,831] Therefore, the incidence of bleeding and severe bleeding differs remarkably between studies. Orthopaedic surgery is often associated with clinically relevant bleeding and the need for allogeneic blood transfusion.[480,534,832–839] The implementation of a blood transfusion protocol (algorithm) together with staff education, based on early preoperative detection and treatment of anaemia, perioperative blood salvage and retransfusion, and a restrictive transfusion trigger, has been shown to reduce allogeneic blood transfusion and the need for preoperative autologous blood donation.[191,243,565,832–836,838–849]

Severe bleeding with the need for allogeneic blood transfusion is relatively uncommon in neurosurgery (affecting 6.7% of patients undergoing neurosurgery in 2010 at University Hospital Essen, Germany; unpublished observations). However, haematoma growth has a major impact on neurological outcomes and mortality in patients with intracerebral haemorrhage (ICH).[850,851] Therefore, ICH has to be treated early.

Recommendation

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections. **B**

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections such as wound infection and pneumonia,[4,399,852–856] increased length of hospital stay, and increased hospital costs.[837,852,856,857]

Recommendation

Infusion of colloids in patients with severe bleeding can aggravate dilutional coagulopathy by additional effects on fibrin polymerisation and platelet aggregation. **C**

Coagulopathy in patients undergoing orthopaedic surgery is usually caused by pre-existing coagulation disorders, medication with oral anticoagulants or antiplatelet drugs, or dilutional coagulopathy due to severe blood loss and volume resuscitation with crystalloids and colloids. Colloids, and especially high molecular weight hydroxyethyl starch (HES) solutions, have dose-dependent effects on fibrin polymerisation and platelet aggregation, aggravating coagulopathy.[30,411,858–864]

8.3.2 Bleeding risk due to pre-existing coagulation disorders and medications

Recommendations

We recommend that, for orthopaedic surgery, monotherapy with aspirin does not need to be discontinued. **1B**

We recommend discontinuing dual antiplatelet therapy before urgent intracranial neurosurgery. A risk-benefit analysis is required for the continuation of aspirin monotherapy during neurosurgery. **1B**

COX-2 selective NSAIDs do not increase perioperative blood loss in patients undergoing total knee arthroplasty.[835,865–867] Therefore, it is not necessary to discontinue these drugs before surgery. In contrast, ibuprofen, diclofenac and indomethacin significantly increase perioperative blood loss in total hip arthroplasty.[835,866–868] Therefore, discontinuation of non-selective NSAIDs is advised.

Pretreatment with daily low-dose aspirin was associated with a small increase in postoperative transfusion but no major bleeding in patients undergoing proximal femoral fracture surgery.[869–872] Neither aspirin nor clopidogrel monotherapy needs to be discontinued before urgent orthopaedic surgery, and surgery should not be delayed in patients receiving such treatment.[872–879]

Recent studies examining the effect of prior antiplatelet therapy on outcome in patients with spontaneous ICH have shown conflicting results.[880] A large, prospective trial demonstrated that antiplatelet medication at ICH onset was not associated with increased haemorrhage volumes, haemorrhage growth, or clinical outcome at 90 days.[881] However, the combination of aspirin and clopidogrel compared to clopidogrel alone after recent ischaemic stroke or transient ischaemic attack has been associated with an increased risk of bleeding events.[882] Antiplatelet therapy, and especially dual antiplatelet therapy, has also been associated with an increased risk of ICH after fibrinolytic therapy in patients with ischaemic stroke.[883] A third study suggested that antiplatelet medication may potentially increase ICH volume.[884] A meta-analysis and systematic literature review reported that antiplatelet therapy at the time of ICH increased mortality but had no effect on functional outcome.[885] Prasugrel is associated with an increased risk of major/fatal bleeding, compared to clopidogrel.[886] Compared to clopidogrel, ticagrelor has been shown to significantly reduce the rate of death from vascular causes, myocardial infarction or stroke, without increasing major bleeding.[887] In another study, there was no significant difference between ticagrelor and clopidogrel in the risk of stroke; however, intracranial bleeding was more common with ticagrelor.[888]

In summary, monotherapy with aspirin or clopidogrel seems not to be associated with a significantly increased risk of ICH or haematoma growth, but dual antiplatelet therapy, therapy with prasugrel, or a combination with other risk factors such as fibrinolytic therapy or VWD increase the risk of ICH and subsequent haematoma growth.[882,883,889] Therefore, dual antiplatelet therapy should be discontinued before urgent intracranial neurosurgery.[876,890] There is need for a risk-benefit analysis of the continuation of aspirin monotherapy during neurosurgery.

Recommendation

We recommend against performing orthopaedic surgery during the first three months after bare metal stent implantation or during the first twelve months after drug-eluting stent implantation. **1C**

Following bare metal stent implantation or drug-eluting stent implantation, elective orthopaedic surgery should not be performed during the first three months or twelve months respectively, because surgery results in a pro-haemostatic condition and increases the risk of stent thrombosis.

8.3.3 Screening tests to predict bleeding in orthopaedics and neurosurgery

Recommendation

Preoperative medication with ADP receptor antagonists or with new oral anticoagulants is associated with an increased risk of major bleeding and ICH, especially if used in combination. **B**

Preoperative administration of ADP receptor antagonists such as clopidogrel, prasugrel and ticagrelor, or new oral anticoagulants such as dabigatran, rivaroxaban and apixaban is associated with an increased risk of major bleeding and ICH, especially if used in combination.[882,886,888,891–894] Of note, these drugs cannot be monitored with conventional coagulation screening tests such as aPTT, PT and platelet count.[895–899]

Recommendation

Reduced platelet activity is associated with early haematoma growth, more intraventricular haemorrhage and worse 3-month outcome following ICH. **C**

Conflicting evidence exists as to whether the direct thrombin inhibitor dabigatran enlarges haematoma volume in experimental ICH.[900,901] However, a recent case report has reported the development of an epidural haematoma and severe intraoperative haemorrhage in a spine trauma patient on dabigatran.[902] Furthermore,

neuraxial blockade is contraindicated in patients on dabigatran, even 34 h after withdrawal of the drug.[903]

Conflicting data also exist regarding whether or not prior antiplatelet therapy has an impact on haemorrhage growth or outcome after ICH and traumatic brain injury.[880,881,884,901,904,905] A recently published meta-analysis including a 25 cohort multivariate analysis showed that antiplatelet therapy at the time of ICH, compared to no antiplatelet therapy, was independently associated with increased mortality but not with poor functional outcome.[885] Furthermore, cerebral microbleeds are a potential risk factor for ICH in patients treated with antiplatelet drugs or warfarin.[906–908]

The efficacy of platelet transfusion in patients on antiplatelet therapy suffering from ICH or traumatic brain injury is also currently under discussion.[880,909–911] Conflicting data exist concerning the impact of antiplatelet drugs on ICH growth on one hand, and the efficacy of platelet transfusion to stop bleeding on the other, and can in part be explained by the variable response to antiplatelet drugs. Several authors reported a close correlation between platelet function testing using ADP as an activator in whole blood impedance aggregometry (Multiplate) or whole blood turbidimetric aggregometry (VerifyNow) and bleeding complications, transfusion requirements for platelet concentrates and outcome after ICH.[912–916] In addition, reduced platelet activity has been associated with early haematoma growth, more intraventricular haemorrhage and worse 3-month outcome after ICH.[917,918] Therefore, point-of-care testing of platelet function may be helpful to detect platelet dysfunction in patients with ICH or prior to neuraxial surgery or blockade, and to guide corresponding therapy.[914,919–922] Also, thrombin time and ecarin clotting time may be helpful to identify emergency patients treated with oral direct thrombin inhibitors such as dabigatran.[896,898,923]

Recommendation

Low platelet count, low plasma fibrinogen concentration and FXIII deficiency are predictive of bleeding complications in ICH, intracranial surgery and major spine surgery, particularly when they occur in combination. **C**

In a multivariate analysis of predictors of haematoma enlargement in spontaneous ICH, a low concentration of fibrinogen ($2.41 \pm 0.08\,g\,l^{-1}$ vs. $2.86 \pm 0.04\,g\,l^{-1}$ in patients with and without haematoma growth, respectively) was the only haematological parameter shown to be an independent predictor of haematoma growth, with an odds ratio of 0.74 for one standard deviation change ($0.09\,g\,l^{-1}$; $P = 0.042$).[924]

Most guidelines recommend a transfusion threshold of $100\,000\,\mu l^{-1}$ platelets in patients undergoing neurosurgery, based on expert opinion.[925–929] However, in a prospective observational study in patients undergoing intracranial surgery, a postoperative platelet count below $150\,000\,\mu l^{-1}$ was associated with a 2.5-fold increase in relative risk of postoperative haematoma requiring revision surgery, and in combination with FXIII activity <60%, the relative risk for haematoma increased to 9.7.[410] In the same study, preoperative FXIII activity <80% was associated with a 3.9-fold increase in relative risk of postoperative haematoma requiring revision surgery, which increased to 6.4-fold for postoperative FXIII activity <60%.[410] The third risk factor was fibrinogen concentration of $<3.0\,g\,l^{-1}$ preoperatively or $<1.5\,g\,l^{-1}$ postoperatively, with a 2.9- and 2.5-fold increased relative risk of postoperative haematoma respectively. The highest relative risk of postoperative haematoma (12.2-fold) was achieved with the combination of a postoperative FXIII activity <60% and fibrinogen concentration $<1.5\,g\,l^{-1}$. A postoperative prolongation of PT (<60% activity compared to normal; relative risk, 6.2) or aPTT (>35 s; relative risk, 4.8) had less impact on the relative risk for postoperative haematoma, even in combination with low FXIII activity (<60%).[410]

FXIII activity cannot be measured by conventional coagulation screening tests. Of note, in a study determining the effect of colloid infusion (HES 200/0.5 or modified gelatin 4%) on haemostasis in patients undergoing knee replacement surgery, the activity of FXIII decreased from 89.0 to 58.5%.[860] Acute diffuse postoperative bleeding due to acquired FXIII deficiency has also been reported after free flap operations in plastic surgery.[930] Furthermore, there are several case reports dealing with spontaneous subdural haematomas or recurrent spontaneous ICH in children and young adults related to FXIII deficiency.[931–933] Prophylactic therapy with a FXIII concentrate in young patients with congenital FXIII deficiency was associated with a marked decrease of bleeding episodes.[934–936] Furthermore, some FXIII polymorphisms are associated with an increased risk of aneurysmal subarachnoid haemorrhage.[937,938] In summary, FXIII seems to play an important role in postoperative bleeding complications in neurosurgery.

Recommendation

Preoperative measurement of plasma fibrinogen concentration provides more information on bleeding volume and transfusion requirements than standard screening tests. **C**

Preoperative plasma fibrinogen concentration has been shown to be strongly associated with increased perioperative bleeding and transfusion requirements (>2 U RBC) in scoliosis surgery.[939] In this prospective observational study, total blood loss correlated significantly with preoperative fibrinogen concentration but with neither platelet count, aPTT nor PT. Patients with blood loss in the upper quartile had significantly lower preoperative

plasma fibrinogen concentrations (2.6 ± 0.6 vs. $3.1 \pm 0.6\,g\,l^{-1}$; $P = 0.002$). Patients undergoing extensive transfusion (>2 U RBC) had significantly lower preoperative fibrinogen plasma concentrations (2.5 ± 0.7 vs. $3.1 \pm 0.6\,g\,l^{-1}$; $P = 0.002$), while preoperative platelet count, aPTT, and PT did not differ. These results indicate that preoperative fibrinogen concentration is a limiting factor for postoperative haemostasis during and after scoliosis surgery. Preoperative measurement of fibrinogen concentration provides more information on blood loss and transfusion requirement than standard screening tests.[939]

Recommendation

We suggest the use of viscoelastic tests (ROTEM/TEG) for monitoring perioperative haemostasis in major orthopaedic surgery and neurosurgery. **2C**

Hypocoagulability in thrombelastography (prolonged r and k time, reduced α-angle and maximum amplitude) has been shown to be associated with an increased incidence of bleeding complications in paediatric neurosurgical patients, whereas standard coagulation tests (platelet count, PT, aPTT, and plasma fibrinogen) were not.[940] However, pre-, intra- and postoperative fibrinogen concentrations were $>3\,g\,l^{-1}$ in both groups in this study. In several studies, thromboelastometry (FIBTEM test) has been shown to successfully diagnose fibrinogen deficiency, as well as fibrin polymerisation disorders, such as those induced by colloid infusion or dysfibrinogenaemia.[30,40,123,411,427,862,864,941–943]

Recommendation

The intensity of oral anticoagulation with warfarin, measured by INR, shows a close correlation to the incidence and severity of bleeding complications, in particular with ICH. **C**

The incidence of ICH in patients on oral anticoagulation with warfarin has been reported at 0.1%–3.7% per patient-year, and the incidence of major bleeding at 1.2–13.1% per patient-year. Independent risk factors for major bleeding and ICH have been identified as the indication for oral anticoagulation (e.g. atrial fibrillation or cerebral ischaemia), the patient's age (≤65, 66–85 or >85 years) and the intensity (INR) and duration of anticoagulation.[944–950] Patients anticoagulated with warfarin because of cerebral ischaemia had 19 times the risk of ICH compared to patients with atrial fibrillation.[945] The incidence of ICH was twice as high for patients >65 years of age, and around two times higher again in patients >85 years of age.[945,947] An INR of 1.6–2.0 was associated with insufficient anticoagulation,[946,948] whereas an INR of 2.0–3.0 is considered as effective and safe.[946,949] However, the incidence of ICH increased significantly with INR values >3.0;[946–949,951] here, the incidence of ICH increased by a factor of 1.37 for each increase of INR by 0.5, and the risk for death increased 2.3 times for each increase of INR by 1.[945,949] Furthermore, patients with INR >3.0 had a significantly greater haematoma volume and a higher mortality.[952] In summary, the intensity of oral anticoagulation with warfarin, measured by INR, shows a close correlation to the incidence and severity of bleeding complications, in particular to ICH.

8.3.4 Antifibrinolytics

Recommendations

We suggest administering tranexamic acid in total hip arthroplasty, total knee arthroplasty, and major spine surgery. **2A**

Tranexamic acid may promote a hypercoagulable state for some patients (with pre-existing thromboembolic events, hip fracture surgery, cancer surgery, age over 60 years, women). Therefore, we suggest an individual risk-benefit analysis instead of its routine use in these clinical settings. **2A**

Antifibrinolytic medication has been shown to reduce perioperative blood loss, allogeneic blood transfusions and associated costs in major orthopaedic surgery such as total hip or knee arthroplasty.[477,953–955] Although concerns exist about increased thrombotic events with the use of these agents, large meta-analyses suggest that tranexamic acid can be employed safely and efficaciously to decrease perioperative blood loss and transfusion requirements without increased risk of thromboembolic complications in major orthopaedic surgery.[480,534,645,953,954,956–958]

However, further studies are needed to clarify the neurological risk, appropriate indications and dosing of tranexamic acid.[653] In addition, the use of antifibrinolytics in patients with cancer cannot be recommended, because no beneficial effect has been shown and the risk of thromboembolic complications may be increased.[959,960] Tranexamic acid may also promote hypercoagulability following pre-existing thromboembolic events and hip fracture surgery, in patients over 60 years, and in women.[961]

Data showing favourable efficacy and safety are best for tranexamic acid,[480,954,962] whereas in comparison, the data for EACA are sparse.[477,529,531,963–967] In several RCTs, hip/knee replacement patients received tranexamic acid as a single preoperative intravenous bolus dose of $10–15\,mg\,kg^{-1}$.[535,538,968–972] In some RCTs, a second dose was given 3 h later or at the time of tourniquet deflation,[531,973–975] while in others a continuous infusion of $1\,mg\,kg^{-1}\,h^{-1}$ was started after the initial bolus.[530,976–979] Oral administration of tranexamic acid (1 g preoperatively and then every 6 h for 18 h postoperatively) has also been shown to be effective in patients with total knee replacement.[980] In hip fracture surgery, tranexamic acid ($15\,mg\,kg^{-1}$ as a single or double bolus dose at surgical incision and 3 h later) reduces allogeneic

blood transfusion but may promote hypercoagulability.[532,961,981] Thus, further safety evaluation is required before recommending routine use of tranexamic acid in this setting. In several RCTs performed in children and adults undergoing scoliosis/spine surgery, a loading dose of 10–30 mg kg^{-1} tranexamic acid followed by a continuous infusion of 1 mg kg^{-1} h^{-1} has been shown to be effective and well tolerated.[904,982,983] EACA has been administered to scoliosis surgery patients (loading dose 100 mg kg^{-1} followed by 10 mg kg^{-1} h^{-1} until the end of surgery).[966]

In neurosurgery, 1 g tranexamic acid immediately after the diagnosis of aneurysmal subarachnoid haemorrhage, followed by 1 g every 6 h until the aneurysm was occluded, reduced mortality from early rebleeding by 80%.[984] However, data on the efficacy and safety of antifibrinolytics in intracranial surgery are sparse and relate mainly to aprotinin, which was withdrawn in 2007.[985]

8.3.5 Recombinant activated factor VIIa

Recommendations

We suggest the use of rFVIIa in patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery. **2C**

Prophylactic use of rFVIIa does not reduce perioperative blood loss or transfusion in non-haemophiliac and non-coagulopathic patients undergoing major orthopaedic surgery or neurosurgery, and it may increase the incidence of thromboembolic events. Therefore, we recommend against the prophylactic use of rFVIIa in these clinical settings. **1B**

We recommend restricting off-label use of rFVIIa to patients with severe bleeding who are unresponsive to other haemostatic interventions. **1C**

Continuous infusion of rFVIIa (initial preoperative bolus of 90 μg kg^{-1} followed by a continuous infusion of 50 μg kg^{-1} h^{-1} for a median of 20 days) was effective and well tolerated in a prospective study of patients with neutralising antibodies to FVIII undergoing elective major orthopaedic surgery. Postoperative bleeding was controlled by an additional single bolus of 60 μg kg^{-1} rFVIIa.[986] A recently published consensus protocol for the use of rFVIIa in elective orthopaedic surgery in haemophiliac patients with inhibitors recommended an initial bolus dose of rFVIIa in the range of 120–180 μg kg^{-1} to cover surgery and concomitant use of antifibrinolytic agents and fibrin sealants.[987] Conversely, there is a lack of evidence to suggest that rFVIIa might be effective and well tolerated in severe intractable bleeding during spinal surgery.

rFVIIa reduced intraoperative transfusion requirement for RBCs in 26 adolescent patients with scoliosis, who received rFVIIa perioperatively.[988] Other studies have shown that a small dose of rFVIIa (20 μg kg^{-1}) reduced PT and aPTT but did not significantly reduce blood loss.[989,990] Moreover, the drug failed to produce a significant reduction in blood loss or transfusion volume in an RCT in 49 spinal surgery patients.[991] One patient with advanced cerebrovascular disease who received 30 μg kg^{-1} rFVIIa died six days after surgery due to an ischaemic stroke. In addition, there was also no significant reduction in perioperative blood loss or transfusion of blood components in a randomised, placebo-controlled trial including 48 patients undergoing major pelvic-acetabular surgery.[992] Therefore, there is little evidence to suggest that prophylactic rFVIIa reduces perioperative blood loss or transfusion requirements in major orthopaedic surgery.

In studies of non-haemophiliac, coagulopathic neurosurgical patients, 40–120 μg kg^{-1} rFVIIa rapidly normalised PT (baseline INR > 2) and aPTT within 20 min;[993–995] this allows a shorter transit time to intervention/craniotomy.[996,997] Although rFVIIa can reduce the change in ICH volume, no significant effect on mortality, modified Rankin Scale score or extended Glasgow Outcome Scale score has been demonstrated.[555,557,998–1000] However, a significant increase in thromboembolic adverse events has been observed with rFVIIa (e.g. myocardial infarction, stroke), especially in elderly patients and those with pre-existing vascular diseases.[554–557,717,981,998,999,1001–1003] Furthermore, there is no reliable evidence that haemostatic drugs are effective in reducing mortality or disability in patients with traumatic brain injury.[981,1004–1007] Therefore, the use of rFVIIa in paediatric patients with brain tumours should be restricted to patients with life-threatening bleeding who are unresponsive to conventional treatment.[1008,1009]

8.3.6 Prothrombin complex concentrate and new oral anticoagulants

Recommendations

In patients with INR > 1.5, with life-threatening bleeding or ICH, we recommend that four-factor PCCs (20–40 IU kg^{-1}), supplemented with vitamin K (10 mg by slow intravenous infusion), should be used for rapid reversal of VKAs. **1C**

In patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery, we suggest using activated PCCs (e.g. FEIBA, FVIII inhibitor bypassing agents). **2C**

New oral anticoagulants, such as rivaroxaban and dabigatran, may increase surgical bleeding and ICH growth. We suggest that PCC, FEIBA or rFVIIa may be used as non-specific antagonists in life-threatening bleeding or ICH. **2C**

For life-threatening bleeding or ICH among oral anticoagulation patients receiving VKAs, for INR > 1.5,

guidelines recommend PCCs or rFVIIa for immediate reversal of INR, with co-administration of vitamin K (10 mg by slow intravenous infusion).[45,562,592,598,1010–1015] Despite consistency between recommendations, adherence to them is poor in several countries where FFP is used instead of PCC.[593,595,1016–1020] These data indicate a requirement for education in this field,[1019] potentially including information on the three different types of PCC available with different compositions and different indications.[594,595,1021,1022] Four-factor PCCs are most effective for rapid reversal of VKA-induced anticoagulation because they replace all four vitamin K-dependent coagulation factors (II, VII, IX, and X), and some of them also contain inhibitors such as protein C, S, and Z.[941,1021] Three-factor PCCs are used to treat haemophilia B (in the US) and are used for warfarin reversal where four-factor PCCs are not available (e.g. in Australia).[592,1010,1011,1018,1023–1027] Three-factor PCCs contain little FVII and are less effective in correcting INR.[592,1028–1030] Activated PCCs such as FEIBA® (Baxter Healthcare Corp, USA; FVIII inhibitor bypassing agent) are indicated in patients with haemophilia and antibodies (inhibitors) against FVIII or FIX.[1031–1033] At a median initial dose of 100 U kg^{-1}, FEIBA has been shown to be effective, well tolerated (low incidence of thromboembolic events) and cost-effective in patients with FVIII/FIX inhibitors undergoing major orthopaedic and other surgery.[1031,1032,1034–1038] However, activated PCCs are not used for rapid reversal of VKA-induced anticoagulation.

Compared with FFP, which takes 14–50 h to correct INR, four-factor PCCs provide quicker and more controlled correction of INR (a target INR of 1.2–1.4 can be achieved within 3–30 min) and improved bleeding control.[402,449,586–588,590,591,594,595,906,1014,1015,1017,1021,1030,1039–1045] Recommended doses for emergency VKA reversal in the presence of ICH are 20–40 IU kg^{-1} PCC (0.8–1.6 ml kg^{-1}; fixed or calculated from body weight, baseline and target INR), 15–120 μg kg^{-1} rFVIIa or 15–30 ml kg^{-1} FFP.[403,591,1012,1014] Transfusion-associated circulatory overload and subsequent acute lung injury complications, which occur in 1–8% of hip/knee arthroplasty patients receiving FFP, can be avoided by using PCC.[141,400,401,906,1045–1049] The incidence and extent of haematoma growth are significantly lower in patients receiving PCCs compared with FFP and vitamin K,[850] which is attributable to more rapid reversal of INR. Haematoma growth is associated with poor neurological outcome, and aggressive management of VKA-associated ICH with rapid INR correction appears to translate into improved outcomes following ICH;[1050] however, this is yet to be proved by well-designed RCTs.[1051,1052]

For rapid reversal of VKAs, studies have shown that PCCs have a favourable safety profile, with a low incidence of thromboembolic events.[449,587,588,590,591,596,633,1023,1024,1040,1042,1053,1054] In a recent meta-analysis, only 12 patients (1.4%) treated with PCCs for VKA reversal had a thromboembolic event, of which two were fatal.[1055] The incidence of thromboembolic events was 1.8% in patients treated with 4-factor PCCs and 0.7% in patients treated with 3-factor PCCs, and these data are consistent with other reviews and pharmacovigilance data.[1022,1056] The occurrence of thromboembolic events is not surprising because VKAs are prescribed to patients with a high risk of thrombotic events.[596,1022,1054,1055,1057] Excessive substitution with PCCs should be avoided, and accurate monitoring of coagulation status may allow thrombotic risk to be reduced.[1022,1058,1059] Four patients (1.9%) treated with a solvent/detergent-treated and nanofiltrated four-factor PCC have shown seroconversion for parvovirus B19.[588,590,1055] No other cases of viral transmission or infectious complications after administration of PCCs have been published during the last 15 years.[1043,1055–1057]

In contrast to rFVIIa (100 μg kg^{-1}), 4-factor PCCs (20–40 μg kg^{-1}) not only correct PT, INR and lag time in endogenous thrombin potential, but they also normalise thrombin generation and activity of coagulation factors II, VII, IX and X, while additionally shortening bleeding time and reducing blood loss.[454,1060–1062] A higher dose of PCC (50 μg kg^{-1}) may induce hypercoagulable thrombin generation, potentially increasing the risk of thromboembolic events.[1059,1061] This underlines the need to avoid excessive substitution with PCCs, and may be particularly important in bleeding patients with coagulation factor deficiency due to liver dysfunction.[120,420,457,458,1063–1068] Based on point-of-care thromboelastometric results, four-factor PCCs have been used in combination with fibrinogen concentrate in several cohort studies in trauma, neurosurgery, cardiac surgery, visceral surgery and liver transplantation.[118,120,125,398,576,1058] These studies show significant reductions in transfusion requirements, transfusion-associated adverse events, and thromboembolic events with PCC; however, prospective RCTs are needed for confirmation.

The recent approval of new oral anticoagulants, such as rivaroxaban and dabigatran, is changing the therapeutic landscape.[1057,1069–1072] These drugs may hamper haemostatic management because they cannot be monitored by simple conventional laboratory assays, their pharmacokinetics vary significantly between patients (in particular dependent on age and renal function), they may increase surgical bleeding and ICH growth, and they have no validated antagonists.[893,1073–1080] In some animal models, rFVIIa, FEIBA and PCC partially improved laboratory parameters in animals treated with fondaparinux, rivaroxaban or dabigatran, but it is unclear whether these drugs would be effective in treating bleeding patients.[898,900,1081–1084]

8.4 Visceral and transplant surgery

8.4.1 Should coagulopathy associated with chronic liver disease be corrected before invasive procedures?

Haemostatic changes coinciding with liver disease were traditionally thought to confer bleeding diathesis. Recent data challenge this theory, leading to a concept of 're-balanced haemostasis' in patients with chronic liver disease (CLD).[1085,1086]

8.4.1.1 What is the evidence that haemostasis is 're-balanced' in CLD?

Recommendation

Despite PT, aPTT and INR indicating coagulopathy in CLD, global coagulation tests (thrombin generation and TEG/ROTEM) suggest that haemostasis is balanced in stable CLD. **C**

In CLD, procoagulant concentrations are typically decreased (except FVIII, which is elevated). However, most endogenous anticoagulants (antithrombin, proteins C and S) are also depleted,[1087] maintaining haemostatic balance. Thrombin generation in stable liver disease is similar, or elevated, compared with healthy individuals.[1087,1088]

CLD patients often exhibit thrombocytopaenia and platelet adhesion/aggregation abnormalities. These changes may be counterbalanced by increased VWF levels and reduced VWF-cleaving activity of ADAMTS 13.[1089] Platelet hyperactivity has been reported in cholestatic liver disease.[1090,1091]

Elevated fibrinolysis and clot instability are balanced by increased plasminogen activator inhibitor (PAI-1) levels. PAI-1 levels are high in acute liver failure and cholestatic liver disease; clinically significant fibrinolysis is rare in both conditions.[1092,1093]

'Re-balanced' haemostasis in CLD is reflected in the increasing number of CLD patients undergoing major abdominal surgery without requiring transfusion.[1094] However, as venous thromboembolic events are common in cirrhotic patients, they cannot be considered 'auto-anticoagulated'.[1095]

8.4.1.2 What is the evidence that INR reflects bleeding risk in patients with chronic liver disease?

Recommendation

Mild to moderate prolongation of the preoperative PT and INR do not predict bleeding in patients with CLD. **C**

PT, aPTT and INR are widely used to assess CLD patients preoperatively, although evidence that these parameters predict bleeding risk is poor.[91] Massicotte *et al.*[1094] reported that INR does not predict OLT transfusion requirements and that preoperative INR correction is unnecessary. Observational studies suggest that OLT can be performed without FFP transfusion;[1096] this may be advantageous in avoiding volume overload.[1097]

PT and INR do not reflect bleeding risk in CLD, as the concurrent anticoagulant reduction is not assessed.[1098] Thrombin generation is similar in healthy and cirrhotic individuals, and there is no definite association between INR and bleeding risk among liver disease patients.[1099] In addition, INR values may vary between laboratories, so defining cut-off values is problematic.[1100]

8.4.1.3 Should FFP be used to correct prolonged INR before invasive procedures?

Recommendation

We recommend against the use of FFP for preprocedural correction of mild-to-moderately elevated INR. **1C**

Implementation of practice guidelines is recommended to prevent inappropriate transfusion.[1101] Evidence suggests that FFP should not be administered to non-bleeding patients when INR is ≤ 2. Although PT and INR are often used to guide FFP transfusion, no correlation has been established between degree of coagulopathy and transfusion outcome,[16] nor has optimal FFP dosing been determined.

No randomised studies with clinical endpoints have investigated the effectiveness of FFP transfusion in CLD. Current evidence suggests no benefit in correcting mild-to-moderate INR elevations before invasive procedures in CLD patients.

8.4.1.4 What level of thrombocytopaenia should be tolerated in CLD?

Recommendation

We suggest a platelet count of $\leq 50\ 000\ \mu l^{-1}$ as a threshold for platelet transfusion before liver biopsy. **2C**

The evidence supporting platelet count cutoff values is limited. Moreover, platelet count does not represent platelet function. Current consensus,[1099] with supporting evidence,[1102] suggests that a preoperative platelet count $>50\ 000\ \mu l^{-1}$ may be acceptable. Severe thrombocytopaenia ($\leq 50\ 000$ platelets μl^{-1}) occurs in 1% of patients.[1103] Due to an assumed increased bleeding risk, this value is a common trigger for prophylactic preoperative platelet transfusion.

A platelet count $\leq 50\ 000\ \mu l^{-1}$ may trigger platelet transfusion in cirrhotic patients during active bleeding[929] and is recommended as a threshold for platelet transfusion before liver biopsy, despite limited supporting evidence.[1099]

Thrombocytopaenia ($<150\ 000$ platelets μl^{-1}) occurs in $\geq 75\%$ of liver disease patients,[1104] limiting thrombin generation and potentially increasing bleeding risk.[1102] Among liver disease patients undergoing invasive procedures, bleeding occurred in 31% of cases with severe thrombocytopaenia, and none of those with moderate

thrombocytopaenia.[1104] However, among patients with severe thrombocytopaenia, the prevalence of significant coagulopathy did not differ between those who bled and those who did not.

8.4.1.5 Platelet function in cirrhosis

Recommendations

PFA-100 is not predictive of bleeding risk in cirrhosis. **C**

Bleeding time is influenced by many variables and is not useful to stratify bleeding risk. **C**

Primary haemostasis may function effectively in cirrhosis, and low platelet count alone might not increase bleeding risk.[1089] Primary haemostasis in cirrhosis has been assessed using bleeding time,[1105] where bleeding time increased progressively from Child-Pugh class A to class C. However, the validity of prolonged bleeding time as a risk factor for bleeding in cirrhosis remains uncertain.[1106,1107] Assessment of bleeding risk using the platelet count has been recommended instead.[1108]

Chronic inflammation coupled with increased vWF concentrations may enhance platelet activity in cirrhosis, potentially explaining normal bleeding time measurements in patients with low platelet counts. Alternatively, altered vasoreactivity and/or arterial dysfunction, both well documented in cirrhosis, may explain prolonged bleeding time. PFA-100 closure time is prolonged in cirrhosis, although the prognostic value of this is unknown.[1109]

Anaemia may potentially increase bleeding tendency by impairing platelet function; its impact warrants further investigation.[1110]

8.4.2 Acute liver failure and invasive procedures

Recommendation

We recommend that, in acute liver failure, moderately elevated INR should not be corrected before invasive procedures, with the exception of intracranial pressure monitor insertion. **1C**

Acute liver failure (ALF) is defined by encephalopathy and coagulopathy (INR > 1.5) within 26 weeks of onset of acute liver disease. Severity of coagulopathy is a useful prognostic marker for monitoring hepatic function. A review of >1000 patients with ALF reported a mean INR of 3.8.[1111] Patients are therefore assumed to have a bleeding diathesis, although clinically significant bleeding is rare (around 5%) and TEG results are typically normal.[1093,1112] Haemostatic alterations in ALF differ from those in CLD. Thrombocytopaenia is less common in ALF, pro- and anticoagulant depletion is more severe and fibrinolysis is inhibited due to high PAI-1 concentrations.[1113] TEG clot strength is most influenced by platelet count, followed by fibrinogen concentration, then procoagulant factor levels.[1112] Prophylactic FFP transfusion to correct INR is not justified in ALF and compromises INR as an indicator of liver function.

Coagulopathy is almost always treated in ALF patients before invasive procedures;[1114] however, such practice is not supported by data and there are no evidence-based guidelines recommending an appropriate target INR. Historical consensus suggests a target INR <1.5,[1115] although available data[1112] challenge this. Transfusion-free OLT has been described in patients with ALF, with INR up to 8, and INR does not predict intraoperative blood loss.

PT and INR can be corrected using rFVIIa, which has been used before intracranial pressure monitor insertion. However, the evidence for rFVIIa efficacy in reducing bleeding complications is limited.[1116,1117] Optimal dosing remains uncertain, as does the thrombogenic potential of rFVIIa.[1118] Before invasive procedures, fibrinogen concentrations <1 g l^{-1} should be corrected with cryoprecipitate or fibrinogen concentrate. Platelet count ≥50 000 μl^{-1} is acceptable[1115,1119] and there are no clear guidelines concerning clotting factors. With the exception of intracranial pressure monitor insertion, INR should not be corrected preoperatively.

INR correction with FFP introduces volume overload and haemodilution. Correction of coagulation factor concentrations above 30% requires up to 30 ml kg^{-1} FFP.[403] Plasma exchange plasmapheresis with FFP may correct INR and improve haemostasis.[1120] PCC with vitamin K can rapidly correct markedly elevated PT/INR before urgent invasive procedures.[1065] Further, prospective RCTs are required in this area.

8.4.3 Orthotopic liver transplantation

Median transfusion during orthotopic liver transplantation (OLT) has decreased from 20 to 2 U since the 1980 s. The procedure is now often performed without transfusion, although massive transfusion is still required occasionally. Coagulopathic bleeding may be related to dilutional coagulopathy or hyperfibrinolysis.

The aetiology of liver failure is an independent parameter for predicting massive blood loss.[1121] Fewer bleeding complications are observed in cholestatic liver disease compared with viral or toxic liver disease.[1092] Preoperative PT/INR does not predict the need for transfusion,[1122] whereas preoperative haemoglobin concentration does.[1123]

Practice varies between centres with regard to transfusion thresholds and coagulation monitoring.[1124,1125] The number of RBC units transfused intraoperatively shares an inverse relationship with patient survival,[1126] and guidelines are intended to limit unnecessary transfusion.[1127]

8.4.3.1 Methods to reduce blood loss in liver transplantation

Both RBC and platelet transfusion independently predict poor outcome in OLT.[517] Approaches to minimising

transfusion include normothermia, because hypothermia reduces platelet function and impairs coagulation enzyme activity. Even mild hypothermia (<35.5°C) increases blood loss by 16% and the relative risk of transfusion by 22%.[486]

8.4.3.2 Intraoperative fluid management

Recommendation

Fluid restriction, phlebotomy, vasopressors and transfusion protocols may be associated with low transfusion rates during OLT. **C**

In cirrhotic patients, volume loading only marginally increases cardiac output while portal hyperaemia and bleeding are increased. Low transfusion rates (<80%) during OLT have been reported using fluid restriction, phlebotomy, vasopressors and transfusion protocols.[1128,1129] However, aggressive volume restriction may increase renal dysfunction, limiting its use in some patients.[1130]

When using colloids, third-generation starch solutions are recommended because they have less effect on coagulation and reduce blood loss and transfusion compared with second-generation starches.[863] Patients with end-stage liver disease may exhibit delayed clot formation and reduced clot firmness following even moderate fluid dilution.[1131]

Thrombin generation in OLT patients is usually normal or supranormal,[1086] supporting restrictive FFP transfusion during OLT. If massive bleeding is not evident, FFP transfusion may increase bleeding due to portal hyperaemia.[1097]

8.4.3.3 Intraoperative cell salvage

Intraoperative cell salvage (ICS) has been used to reduce autologous transfusion requirements and provide cost savings for over two decades.[1132] As OLT often involves minimal RBC transfusion, a full ICS setup is not always justifiable. Thus, it is recommended that a 'stand by' setup is available. Washed erythrocytes lack clotting factors and platelets, so transfusion therapy must be tailored accordingly. Heparin anticoagulation of salvaged blood appears safe because washed cells contain minimal heparin. Alternatively, citrate may be used.

UK guidelines[1133] state that ICS may be considered for hepatocellular tumour surgery if there is a significant risk of major bleeding. Risk of malignant cell reinfusion should be balanced against risk of allogeneic transfusion-related complications. Leukodepletion filters reduce reinfusion risks[1134] but also reduce reinfusion speed. OLT studies have not shown any risk of bacterial contamination. During ICS, blood should be collected only after ascitic fluid has been removed and should cease once biliary anastomosis begins.

8.4.4 Coagulation monitoring

Differences between centres in coagulation monitoring contribute to variations in OLT transfusion practice.[115] Laboratory-based coagulation tests are unsuitable because of slow turnaround times and inability to diagnose hyperfibrinolysis.[1135]

8.4.4.1 Global coagulation tests: thrombelastography (TEG)/thromboelastometry (ROTEM)

Recommendation

We recommend the use of perioperative coagulation monitoring using ROTEM/TEG for targeted management of coagulopathy. **1C**

TEG monitoring can reduce transfusion requirements by 30%.[1136,1137]. However, high quality data supporting the effectiveness of such practice is lacking.[1138] In a Cochrane review of TEG/ROTEM haemostatic monitoring,[17] only one RCT related to liver transplantation[133] and this was not blinded. Other evidence suggests TEG/ROTEM monitoring may help reduce bleeding and transfusion of FFP and platelets in liver transplantation.[1139] As RBC and platelet transfusions are associated with increased mortality, TEG/ROTEM could help to improve patient outcomes; however, larger trials are required to investigate this.[519,1127]

TEG/ROTEM can facilitate targeted management of specific coagulopathies, potentially reducing transfusion requirements.[134,1137] Diagnostic capability is maximised using different activators and modifiers (described elsewhere in this guideline – see section 4.2.3.2). TEG/ROTEM can identify hyperfibrinolysis, indicating antifibrinolytic therapy.[1140] In addition, the FIBTEM test can guide administration of fibrinogen concentrate or cryoprecipitate,[1058] in turn reducing platelet and RBC transfusions.[1141]

A heparin effect is commonly evident during reperfusion, due to heparin administered to the donor and endogenous vascular endothelial heparinoids.[1140] Reversal with protamine is rarely indicated because the effects of the heparin are temporary and do not usually increase bleeding risk.[1142]

8.4.5 Pharmacological therapy

8.4.5.1 Antifibrinolytic drugs

Recommendation

Antifibrinolytic therapy reduces blood loss and transfusion requirements in liver transplantation. **B**

We recommend antifibrinolytic drugs for treatment of fibrinolysis (evident from microvascular oozing or TEG/ROTEM clot lysis measurement) and not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis following reperfusion. **1C**

Lack of tissue plasminogen activator (tPA) clearance increases fibrinolysis during OLT.[1143] Dramatically elevated levels of tPA follow reperfusion, causing explosive primary hyperfibrinolysis[1144] and, potentially, diffuse bleeding. Hyperfibrinolysis typically subsides within an hour but may persist with poorly functional or marginal grafts.[1145] This scenario rarely occurs in ALF due to elevated PAI-1. Antifibrinolytic drugs have been used prophylactically and therapeutically for TEG-determined fibrinolysis.[1137,1146]

A Cochrane review demonstrated that antifibrinolytic therapy helps to reduce blood loss and perioperative allogeneic blood transfusion.[480] Tranexamic acid and EACA were generally as effective as aprotinin. Aprotinin was not associated with increased risk of vascular occlusion and death,[1147] but an increased risk of renal failure could not be excluded.[480] An observational study involving OLT patients found a significant risk of transient renal dysfunction with aprotinin, but no increase in renal failure or mortality.[1148]

A meta-analysis of antifibrinolytic drugs concluded that both aprotinin and tranexamic acid reduce RBC transfusion in OLT.[476] Aprotinin, but not tranexamic acid, also reduces intraoperative FFP transfusion. There was no evidence of antifibrinolytic therapy increasing risks of hepatic artery thrombosis, venous thromboembolism or mortality. Similarly, a review of over 1400 OLT patients found no difference in arterial or venous thromboembolism between patients receiving aprotinin and no treatment.[1149] However, this does not preclude risks in specific patient subgroups or with specific doses. EACA is widely used in the USA despite the existence of only one RCT, and this study demonstrated no benefit versus placebo.[547]

As massive bleeding has become less frequent during OLT, there have been moves from routine to selective antifibrinolytic prophylaxis (high-risk patients), and onto treatment only. Predicting hyperfibrinolysis is problematic because bleeding is greatly influenced by the donor liver, which is not reflected in preoperative assessment.[1150] Treatment using tranexamic acid/EACA is recommended if microvascular oozing or fibrinolysis is evident. Timing and degree of fibrinolysis is important; non-severe fibrinolysis occurring after reperfusion may resolve spontaneously.[1066] Lowest effective doses are uncertain; tranexamic acid is currently given in 1–2 g increments.

Recombinant activated factor VII

Recommendation

We recommend against rFVIIa for prophylaxis; rFVIIa should be used only as rescue therapy for uncontrolled bleeding. **1A**

Two RCTs have investigated prophylactic rFVIIa in OLT:[1151,1152] both demonstrated correction of INR but no reduction in transfusion. Off-label 'rescue' therapy with rFVIIa may help to control haemorrhage. However, systematic reviews show no reduction in mortality and increased risk of arterial thromboembolism.[554,717]

8.4.6 Pulmonary emboli and intracardiac thrombi in orthotopic liver transplantation

Perioperative intracardiac and pulmonary emboli are rare but potentially lethal complications of OLT. A systematic review reported an incidence of 1% and mortality of 68%.[1153] The aetiology is uncertain but unlikely to be causally related to venovenous bypass or antifibrinolytics. One study described a 1.9% incidence of intracardiac thrombi (ICT), mostly in association with reperfusion.[1154] Portal hypertension and intraoperative haemodialysis were independent risk factors. Routine intraoperative transoesophageal monitoring is recommended to identify ICT. ICT has been linked with hypercoagulability according to TEG, even when conventional tests suggest hypocoagulability.[1155] In addition, the value of thromboelastometry was demonstrated in a fatal cardiopulmonary embolism following aprotinin therapy.[1156]

Postoperative LMWH prophylaxis for thromboembolic complications is not administered universally. However, accumulating evidence supports LMWH prophylaxis and extended postoperative coagulation monitoring.[1157]

8.4.7 Antiplatelet therapy and platelet function testing

Recommendation

POC platelet function tests may help to stratify risk and rationalise platelet transfusion in patients taking antiplatelet drugs. **C**

A small number of OLT patients receive antiplatelet therapy for prevention of coronary/cerebral vascular disease or for coronary stent insertion. An observational study involving coronary stented patients undergoing cardiac surgery reported that although the risks of major bleeding decreased, the risk of major adverse cardiac and cerebrovascular events increased if antiplatelet therapy was interrupted for more than 5 days preoperatively.[1158] In emergency surgery or OLT, prior therapeutic interruption is not feasible.

The degree of platelet inhibition is variable; 'hyporesponders' may be at increased risk of ischaemic events, while 'hyper-responders' may have increased risk of bleeding.[1159] Bleeding risk may be stratified using point-of-care platelet function analysers: minimal risk is associated with platelet inhibition <30%, but >60% inhibition with 2- to 6-fold increased risk.[1160] Cardiac surgery patients with high platelet inhibition appear to have increased bleeding risk and increased transfusion requirements. Patients in the lower tertile of platelet aggregation (measured using multiple electrode aggregometry) receive more platelet concentrate than upper

tertile patients.[159,186] Similarly, the m-TEG platelet mapping assay (Haemonetics, Braintree, MA) has shown that >70% inhibition increases bleeding risk.[1161] Platelet mapping has been used to guide antiplatelet therapy in a Budd-Chiari patient with an occluded transjugular intrahepatic portosystemic shunt.[1162] Tranexamic acid may partially reverse the effect of antiplatelet therapy.[72]

Platelet function tests may potentially predict platelet transfusion requirements although no 'gold standard' test or cut-off value has yet been established. Studies are ongoing.[1163]

8.4.8 Liver resection

Blood loss during liver resection is a major determinant of perioperative outcome. Selective vascular occlusion techniques help to control blood loss, with complete vascular occlusion employed in excessive bleeding. Intermittent clamping or ischaemic preconditioning may reduce ischaemic liver injury.[1164]

8.4.8.1 Haemodynamic interventions to reduce blood loss

Recommendation

A low central venous pressure and restrictive fluid administration reduce bleeding. **B**

Fluid restriction and maintenance of low central venous pressure (CVP) during hepatic resection reduce blood loss.[1165] However, low CVP may increase complications including air embolism and renal failure.[1166] It is uncertain whether fluid restriction during hepatic resection increases the risk of renal dysfunction, although this risk is generally considered minimal.

8.4.8.2 Pharmacological interventions to reduce blood loss

Recommendation

We suggest that antifibrinolytic drugs should be considered in cirrhotic patients undergoing liver resection. **2C**

A Cochrane review reported reduced allogeneic transfusion in patients receiving aprotinin or tranexamic acid.[1165] Desmopressin, rFVIIa and AT did not decrease transfusion. However, because all of the studies had a high risk of bias (likely type I and type II errors), no general recommendations can be made without further large trials. A separate systematic review showed no difference between rFVIIa and placebo.[467]

8.4.9 Acute upper gastrointestinal bleeding

In decompensated CLD, bleeding is often triggered by haemodynamic alterations arising from portal hypertension, endothelial dysfunction, renal failure, bacterial infection, endogenous heparinoids[1167,1168] and DIC. Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency, with a mortality in excess of 7%.[1169]

8.4.9.1 Acute variceal bleeding

Recommendations

We recommend that acute variceal bleeding should be managed by a multidisciplinary team. A specific multimodal protocol for upper gastrointestinal haemorrhage should be available. **1C**

We recommend that early treatment involves immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding and early interventional endoscopy. Antibiotics must be started on admission. **1A**

Variceal bleeding is a major complication of portal hypertension and a leading cause of death in cirrhosis. Although management and prognosis have improved,[1170] early mortality following acute variceal bleeding (AVB) remains high (15–24%).

AVB outcomes can be improved by experienced multidisciplinary management and immediate interventional endoscopy.[1170] Early risk assessment (Rockall scoring system or Blatchford score) is important. Combined pharmacological and endoscopic intervention is recommended for initial treatment of acute bleeding. Vasoactive drugs (preferably somatostatin or terlipressin) may improve control of haemorrhage and should be given immediately if variceal bleeding is suspected, with maintenance for 2–5 days.[1171]

Following stabilisation with fluid and blood support, emergency diagnostic endoscopy and endoscopic variceal treatment should be performed by a skilled endoscopist. Antibiotic prophylaxis forms an integral component of AVB treatment, commencing at admission and maintained for ≥7 days.[1172] For acute refractory bleeding, rescue therapy should begin immediately. Balloon tamponade may be necessary and shunt therapies are often effective if initial treatment fails.

8.4.9.2 Fluid Resuscitation and pharmacological interventions

Recommendations

Tranexamic acid reduces mortality but not rebleeding. **B**

rFVIIa should be used only as rescue therapy; we recommend against its routine use. **1C**

Blood volume resuscitation should be undertaken as soon as possible with the aim of maintaining systolic blood pressure at around 100 mmHg. Optimal volume replacement remains controversial. No high-quality RCTs have compared crystalloids with colloids in patients with UGIB; however, in critical care, a meta-analysis and a large RCT suggest no differences between them.[1173,1174] Conservative volume replacement and transfusion is recommended. Because colloids remain intravascular for longer and reduce the total administration volume, they may be preferable. Vasoactive drugs have been shown to counteract portal pressure increases induced by volume expansion.

Blood transfusion should generally aim to maintain haemoglobin at 7–8 g dl^{-1}. Abnormal PT/INR and platelet count correlate poorly with bleeding and TEG may provide more useful information.[1175,1176] In active bleeding, FFP should be given to maintain INR < 2 and platelets given to maintain platelet count >60 000 μl^{-1}.[1102] The value of antifibrinolytic drugs in treating UGIB is unclear. Meta-analyses suggest that tranexamic acid does not lower rates of rebleeding or surgery, but that it reduces mortality (relative risk 0.61);[1177,1178] large RCTs are needed to confirm these findings.

PT can be corrected using rFVIIa in CLD patients with UBIG. Benefits over standard therapy are not evident,[1179] although a possible indication exists in uncontrolled bleeding.[1180] European guidelines on rFVIIa recommend against its use in elective liver surgery or bleeding episodes in patients with Child-Pugh A cirrhosis. Efficacy in Child-Pugh B and C is uncertain and thromboembolic events remain a concern.[1181]

8.4.10 Coagulopathy and renal disease

Patients with chronic kidney disease (CKD) have haemostatic derangement with variable clinical manifestations.[1182] As CKD advances, procoagulant abnormalities (impaired tPA release, increased PAI-1, elevated fibrinogen and increased TF/FVIII) persist.[1183] Patients also develop platelet dysfunction, comprising impaired GPIIb/IIIa receptor function, altered release of ADP and serotonin from platelet granules, and faulty arachidonic acid and prostacyclin metabolism.[1184] Uraemic toxins may stimulate nitric oxide release, exacerbating platelet dysfunction. Correction of anaemia in CKD patients may improve platelet function.[1185]

8.4.10.1 Assessment of platelet function in chronic kidney disease

Recommendation

Point-of-care tests of platelet function and bleeding time provide no reliable platelet function assessment in uraemia and no prediction of bleeding in this setting. **C**

CKD patients typically have normal/slightly reduced platelet counts. Skin bleeding time (SBT) has been used to assess platelet function, but this has poor reproducibility. The PFA-100 has better sensitivity and specificity than SBT.[1186] However, correlation has not been shown between PFA-100 closure times and bleeding complications after percutaneous renal biopsy.[1187] A review of point-of-care platelet function tests found inconsistent results, so the authors could not recommend any single test for bleeding risk assessment.[1188]

8.4.10.2 Correction of bleeding diathesis and treatment of bleeding in patients with renal failure

Recommendations

We suggest that conjugated oestrogen therapy should be used in uraemia. **2C**

We suggest that desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. **2C**

There is no evidence to support use of rFVIIa in this setting.

Bleeding complications are common in acute and chronic renal failure.[1189] Modern dialysis techniques, combined with correction of anaemia using erythropoietin, have reduced spontaneous haemorrhage, although bleeding diathesis remains a problem in uraemic patients undergoing invasive/surgical procedures. Several measures are available to reduce bleeding risk in advanced CKD patients:

1. Renal replacement therapy (peritoneal dialysis or haemodialysis) improves platelet function by removing uraemic toxins.[1185]
2. Correction of anaemia in CKD with erythropoietin helps to prevent uraemic bleeding. Increased erythrocyte numbers improve platelet function,[1190] and decreased haemoglobin concentration may intensify platelet dysfunction.[1191]
3. Desmopressin can treat platelet dysfunction in uraemic patients. Desmopressin induces VWF release, improving platelet adhesion/aggregation. Desmopressin shortens bleeding time within 1 h, with effects lasting 4–8 h,[1192] and a single dose of 0.3 $\mu g\,kg^{-1}$, intravenously or subcutaneously, is effective. Doses of 3 $\mu g\,kg^{-1}$ can also be administered nasally. Desmopressin is effective as both prophylaxis and treatment of perioperative bleeding.[1193,1194]
4. Cryoprecipitate has been used to treat uraemic bleeding. It is effective 1 h after infusion, with maximum effect after 4–12 h. Up to 50% of uraemic patients fail to respond to cryoprecipitate. Cryoprecipitate carries a risk of pathogen transmission and is rarely used in CKD.[1182]
5. Conjugated oestrogens may reduce bleeding in uraemic patients,[1195] particularly those with gastrointestinal or intracranial bleeding or undergoing major surgery. An oral dose of 25 mg normalises SBT for 3–10 days.[1196] Low dose transdermal oestrogen (oestradiol 50–100 μg per day) reduces gastrointestinal bleeding and improves bleeding time.[1197]
6. Tranexamic acid shortens bleeding time in uraemic patients. However, it may accumulate in patients with renal insufficiency and there is no evidence of superiority over other therapies. Therefore, tranexamic acid should be considered only in the acute setting when other treatments have proved unsatisfactory.[1185]
7. Anecdotal reports suggest that rFVIIa may control bleeding in uraemic patients.[1198] However, there are no data supporting its safety, efficacy or dosing in this setting.

8.5 Paediatric surgery

8.5.1 Introduction

Severe perioperative bleeding in paediatric patients has typically been treated as it is in adults. Despite developmental changes in the coagulation system, haemostatic capacity is excellent in newborns and children.[1199–1201] Nonetheless, recognition of these developmental changes may improve the management of acquired paediatric coagulopathy.

8.5.2 Coagulation monitoring

Recommendation

We suggest the use of perioperative coagulation analysis using viscoelastic point-of-care monitoring (ROTEM/TEG) for timely detection of coagulation defects including dilutional coagulopathy and hyperfibrinolysis. **2C**

Diagnosing paediatric perioperative coagulopathy requires rapid, robust coagulation monitoring, alongside age specific reference ranges.[1202–1205] ROTEM and TEG can complement standard coagulation tests, especially in the perioperative setting.[35,114,1136,1206,1207] In a meta-analysis, TEG- or ROTEM-guided transfusion was shown not to affect overall mortality in patients with severe bleeding, but it was associated with significantly reduced bleeding.[17] Data supporting the effectiveness of ROTEM/TEG-guided paediatric coagulation therapy are limited.[427,940,1208–1210]

8.5.3 Fluid resuscitation

Recommendation

No clear recommendation can be made regarding the choice of perioperative fluid replacement in children. **C**

Despite age-dependent variations in coagulation factor levels, the pathophysiology underlying paediatric perioperative bleeding is comparable to adults. Dilutional coagulopathy is encountered in adults and children alike.[427,943,1211–1213] However, a negative impact of colloids on haemostasis should be considered and closely monitored. Cardiopulmonary bypass may cause additional haemostatic disturbances, including platelet dysfunction and excessive fibrinolysis.[1213]

Fluid resuscitation can cause dilutional coagulopathy.[1214–1216] Pronounced coagulation disturbance following HES infusion[1214,1216] and minor disturbances following gelatin solution or albumin[1214] have been reported. A meta-analysis suggests that colloids are no more effective than crystalloids for reducing mortality in critically ill adults.[1217] Together, no clear recommendation can be made regarding choice of fluid for paediatric perioperative resuscitation.

8.5.4 Red blood cell transfusion

Recommendation

We suggest that a critical haemoglobin threshold of 8 g dl^{-1} for RBC transfusion may be safe in severe paediatric perioperative bleeding. **2C**

Haemoglobin concentrations vary with age and gender, and RBC transfusion should be tailored accordingly. The required transfusion volume can be calculated as: body weight (kg) x desired increment in haemoglobin concentration (g dl^{-1}) x 5.[1218] In massive bleeding, haemoglobin concentrations should be maintained at $\geq$8 g dl^{-1},[1219] while in stable, critically ill children, 7 g dl^{-1} may suffice.[1220]

8.5.5 Platelet transfusion

Recommendation

We suggest that transfusion of platelet concentrates may be considered if platelet count is <50 000–100 000 μl^{-1}. **2C**

In children and adults, transfusion thresholds for platelets vary according to the type of surgery and platelet functionality. Current data suggest maintaining platelet count at $\geq$50 000–100 000 μl^{-1}.[1221] Transfusion of one unit of platelet concentrate per 10 kg body weight, or 5 ml kg^{-1} of apheresis platelet concentrate, should raise platelet count by 20 000–50 000 μl^{-1}.

8.5.6 Fresh frozen plasma

Recommendation

No clear recommendation can be made regarding the indication and dosing of FFP transfusion in bleeding children, but severe risks have been reported. **C**

Transfusion of FFP for treatment of severe bleeding is recommended by several guidelines but is not supported by high quality evidence.

No randomised, controlled trials have demonstrated that FFP controls paediatric perioperative bleeding. Prophylactic FFP in preterm babies appears not to reduce mortality or disability associated with haemorrhagic/ischaemic brain injury.[1222] Intraoperative FFP transfusion during paediatric craniofacial surgery may not reduce RBC transfusion or blood loss compared with albumin,[1223,1224] although other results do suggest improved postoperative coagulation.[1225] UK guidelines recommend avoiding FFP for simple volume replacement[1226] and one UK study questioned the overall clinical benefits of FFP.[405]

Guidelines typically recommend 10–15 ml kg^{-1} FFP for adults and children with acquired bleeding and prolonged aPTT or PT (>1.5 times normal).[45,57,1219,1226,1227] However, this may be insufficient to achieve haemostasis,[402,403,1228] and the potential for volume overload may preclude increased dosing. Side-effects of FFP include TRALI[340,1229] an increased mortality in children

with ALI, [1230] transfusion-associated cardiac overload,[1231] sepsis in severely burned paediatric patients,[1232] transfusion-related immunomodulation[346] and multiple organ failure.[396]

8.5.7 Coagulation factor concentrates

Coagulation factor concentrate therapy for congenital disorders[1221,1233] has established the potential for paediatric coagulation factor concentrate therapy in acquired perioperative coagulopathies. However, there is a lack of randomised, controlled trial data in children.

8.5.7.1 Fibrinogen concentrate

Recommendations

We suggest that fibrinogen concentrate (30–50 mg kg^{-1}) or cryoprecipitate (5 ml kg^{-1}) may be used to increase plasma fibrinogen concentrations above trigger values of 1.5–2.0 g l^{-1} or FIBTEM MCF >7 mm in bleeding children. **2C**

We suggest that FFP may be used if no other fibrinogen source is available. **2C**

Fibrinogen is the first clotting factor to reach critically low concentrations during life-threatening haemorrhage in adults and children. European guidelines[45,562] recommend higher thresholds (1.5–2 g l^{-1}) than international guidelines.[1227] Fibrinogen substitution can be performed using cryoprecipitate (5 ml kg^{-1}), but this is not available in all countries due to safety concerns. FFP may not provide an adequate increase in plasma fibrinogen concentrations.[1211]. In contrast, fibrinogen concentrate (30 mg kg^{-1}) has been used effectively to treat fibrinogen deficiency (ROTEM FIBTEM maximum clot firmness ≤7 mm) during paediatric craniofacial surgery.[427] This is supported by evidence from prospective adult studies demonstrating the effectiveness of fibrinogen concentrate in aortic surgery,[116] radical cystectomy[431] and major orthopaedic surgery.[411]

Fibrinogen concentrate has a favourable safety profile.[424,1234]

8.5.7.2 Prothrombin complex concentrate

Recommendation

Data for PCC in children are limited and no dose recommendation can be made. **C**

PCC can help to correct dilutional coagulopathy by increasing thrombin generation.[457,460,664] In adults, 20–30 IU kg^{-1} PCC should be sufficient to increase thrombin potential, but there is no evidence on the safety, effectiveness or optimal dosing of PCC for paediatric perioperative bleeding.

8.5.7.3 Coagulation factor XIII

Recommendation

No recommendation on the use of FXIII concentrate in bleeding children can be made.

Acquired FXIII deficiency appears prevalent in surgical and acute care settings.[437] A randomised trial in adults,[448] together with other investigations,[410,439,443] suggest maintaining FXIII levels above 50–60% of normal during perioperative bleeding. FXIII may be supplemented using FXIII concentrate (20 IU kg^{-1})[1235] or FFP transfusion. No data exist on paediatric FXIII supplementation.

8.5.7.4 Recombinant activated factor VII

Recommendation

We recommend against the use of rFVIIa in children. **1C**

rFVIIa has been described as useful for controlling severe bleeding in cardiac[1236–1238] and neurosurgical procedures in children,[1008,1239] although a prospective, randomised trial in paediatric cardiac surgery showed no difference in blood loss with rFVIIa versus placebo.[1240] Failure of rFVIIa to reduce RBC transfusion requirements has been reported in adult trauma patients.[1241] rFVIIa may be efficacious only if fibrinogen concentration and platelet count are sufficient.[1242] Undirected rFVIIa administration may potentially increase thromboembolic complications.[554,667,717,1243,1244]

8.5.7.5 Desmopressin

Recommendation

We suggest against the routine use of desmospressin in the absence of mild haemophilia A or von Willebrand disease. **2C**

Desmopressin has been shown to provide modest reductions in postoperative blood loss and transfusion requirements, without influencing mortality.[1245] Maximum effects are observed at a dose of 0.3 μg kg^{-1}.[1246] However, paediatric studies in cardiac surgery[1247,1248] and other surgical settings[1249–1251] have shown no reduction in allogeneic blood transfusion after desmopressin administration.

8.5.7.6 Antifibrinolytics

Recommendation

We suggest that perioperative antifibrinolytic therapy should be used to reduce blood loss and transfusion requirements in cardiac and non-cardiac paediatric surgery. **2A**

In paediatric patients undergoing cardiac and scoliosis surgery with high bleeding risk, tranexamic acid markedly reduced perioperative blood loss and RBC transfusion.[534,1252] Similar effects have been reported for tranexamic acid in paediatric craniosynostosis surgery.[537] Optimal dosage remains uncertain, with wide variations in reported loading doses (10–100 mg kg^{-1}) and infusion rates (1–10 mg kg^{-1} h^{-1}). In paediatric cardiac surgery, repeated doses are suggested to be more efficacious than a single bolus.[1253]

9 ANTICOAGULATION AND ANTIPLATELET THERAPY

9.1 Introduction

Antithrombotic therapies have a range of indications and in this section we describe how they are used in anaesthesia and intensive care.

9.2 Antiplatelet agents

Perioperative interruption and maintenance of antiplatelet agents (APAs) are associated with increased cardiovascular or haemorrhagic complications, respectively. Guidelines for perioperative APA therapy are based on small observational studies, case reports and expert opinion, so recommendations are weak. In patients with coronary stents, the main risk factor for stent thrombosis is interruption of APA. If these patients require surgery, the optimum delay between stent implantation and surgery is unclear, as is the need for (or optimal duration of) interruption of APA therapy.

9.2.1 Aspirin

Aspirin and other NSAIDs inhibit platelets by inactivating platelet cyclooxygenase-1 (COX-1). Although the effect is irreversible, NSAIDs are weak antiplatelet drugs because they affect only one of the many platelet activation pathways. Randomised trials have shown that aspirin is effective at doses of 50–100 mg per day. There is no convincing evidence that doses >325 mg per day are more effective in reducing the risk of serious vascular events, and higher doses may increase the risk of adverse events (e.g. thrombotic or gastrointestinal).[1254]

Peak plasma aspirin concentrations occur 30–40 min after ingestion (or 3–4 h for enteric coated aspirin). Platelet function is inhibited within 1 h. The half-life of aspirin is 15–20 min, although platelet inhibition lasts for the lifespan of affected platelets.[1254]

Aspirin is indicated and effective for secondary prevention of vascular events. Long-term aspirin therapy reduces the risk of myocardial infarction, stroke or vascular death among high-risk patients (e.g. those with chronic stable angina, prior myocardial infarction, unstable angina, transient ischaemic attack or minor stroke). In such patients, a major vascular event is avoided in 3–5% of individuals over 30 months.

Recommendations

We recommend that aspirin therapy should continue perioperatively in most surgical settings, especially cardiac surgery. **1C**

Where aspirin withdrawal is considered, we recommend a time interval of 5 days. **1C**

Treatment discontinuation increases thrombotic risk; this risk should always be discussed. Following aspirin withdrawal, aspirin treatment should resume as soon as possible postoperatively to prevent platelet activation. The first postoperative aspirin should be a loading dose, given no later than 24 h after skin closure.

Platelet aggregation is restored approximately 4 days after aspirin discontinuation. Point-of-care testing has demonstrated significant recovery of platelet aggregation within 48 h after aspirin cessation, with baseline values re-established within 5 days.[1255] Experimental studies have reported enhanced platelet aggregation after interruption of aspirin.[1256,1257] Platelet thrombi produced after aspirin withdrawal appear more resistant to physiological fibrinolysis. Aspirin or anticoagulant withdrawal has been linked to myocardial infarction or stroke.

In a cohort of acute coronary syndrome (ACS) patients, Collet *et al.*[1258] reported ACS to be associated with aspirin interruption in 5.4% of patients. Ischaemic events were typically observed 12 days after aspirin withdrawal. Other reports associate aspirin interruption with thrombotic events in patients with a history of coronary heart disease, stroke[1259] and peripheral artery disease.[1260]

Surgical bleeding risk associated with APA therapy has been poorly evaluated. In patients undergoing total hip replacement, preoperative aspirin was associated with only a minor increase in bleeding compared with placebo (Pulmonary Embolism Prevention [PEP] trial).[1261]

Systematic reviews have analysed aspirin-associated bleeding risks in non-cardiac surgery. Burger *et al.*[1262] pooled data from 49 590 patients (14 981 on aspirin). Aspirin increased the rate of bleeding complications 1.5-fold but did not increase their severity (except in intracranial surgery and possibly transurethral prostatectomy). Giannarini *et al.*[1263] showed that continued low-dose aspirin (100 mg per day) in men undergoing transrectal prostate biopsy did not increase the incidence of mild bleeding, although the durations of self-limiting haematuria and rectal bleeding were prolonged.

In patients referred for transurethral prostatectomy, open prostatectomy and transurethral resection of bladder tumour, postoperative bleeding did not differ significantly between patients in whom aspirin was initiated early (24 h) or late (3 weeks) after surgery.[1264] Several other articles report similar findings. In general, aspirin should not be withdrawn perioperatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug. Aspirin is administered preoperatively for most vascular procedures. The Eighth ACCP Guidelines strongly recommend aspirin for carotid endarterectomy; aspirin, 75–325 mg per day should be given preoperatively and continued indefinitely (grade of recommendation: 1A).[1265] Two studies have since been published. Oscarsson *et al.*[1266] conducted a randomised, double-blind, placebo-controlled trial to compare the effect of low-dose aspirin with that of placebo on myocardial damage, cardiovascular and bleeding complications in high-risk patients undergoing non-cardiac surgery.

Aspirin (75 mg) or placebo was given 7 days before surgery and continued until the third postoperative day. One hundred and nine of the patients received aspirin and 111 received placebo. Treatment with aspirin resulted in a 7.2% absolute risk reduction (95% CI, 1.3–13%) for postoperative major adverse cardiovascular events (MACE). The relative risk reduction was 80% (95% CI, 9.2–95%). No significant differences in bleeding complications were seen between the two groups. The STRATAGEM study was a randomised, multicentre, blinded study in which 145 patients in the aspirin group were treated for 10 days preoperatively, and 146 patients were in the placebo group.[1267] No significant difference was observed in either the primary outcome score, or at day 30, in the number of major complications between groups. In addition, no difference in major bleeding was observed. In summary, these studies showed that there was no risk in continuing aspirin perioperatively.

Recommendation

For intra- or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7 x 10^{11} [i.e. two standard concentrates] per 7 kg body weight in adults). **2C**

Severe bleeding in patients on aspirin may require immediate platelet transfusion.[1075]

9.2.2 Thienopyridines: clopidogrel and prasugrel

The thienopyridine derivatives ticlopidine and clopidogrel inhibit ADP-induced platelet activation by binding covalently to the P2Y12 receptor. These agents are more potent than aspirin, although platelet activation remains possible with high concentrations of agonists acting through phospholipase C.

Clopidogrel is absorbed rapidly and metabolised extensively. The main systemic metabolite is the carboxylic acid derivative SR 26334. The plasma elimination half-life of SR 26334 is approximately 8 h.[1254]

Prasugrel is a new thienopyridine agent and a highly potent APA. It requires conversion to an active metabolite before binding to the platelet P2Y12 receptor, and its antiplatelet activity is more rapid, consistent and pronounced than that of clopidogrel.[1254] It is rapidly absorbed and the hepatic CYP system converts it into the active form. The active metabolite concentration peaks 30 min after administration and has an elimination half-life of approximately 3.7 h. Differences in metabolic processing result in higher concentrations of active metabolite and therefore improved inhibition of platelet aggregation with prasugrel compared with clopidogrel.[1254] No data are available regarding perioperative use of prasugrel. Its antiplatelet effect lasts for the platelet's lifespan ($\geq$7 days). Recommendations for clopidogrel should be applicable to prasugrel, except for the duration of withdrawal (no more than 7 days for prasugrel).

Recommendations

Clopidogrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 5 days. **1C**

Prasugrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 7 days. **1C**

We recommend that antiplatelet agent therapy should resume as soon as possible postoperatively to prevent platelet activation. **1C**

We suggest that the first postoperative dose of clopidogrel or prasugrel should be given no later than 24 h after skin closure. We also suggest that this first dose should not be a loading dose. **2C**

Several publications have described perioperative haemorrhagic complications associated with clopidogrel, and the risk may increase when clopidogrel is combined with aspirin. However, such risks may be acceptable if withdrawal is also associated with a high risk of thrombotic complications.

A study of clopidogrel in healthy volunteers showed high interindividual variability in platelet inhibition during treatment and recovery of platelet function after discontinuation. This may be explained in part by genetic polymorphism of CYP450 involved in the metabolism of clopidogrel. A low level of inhibition of platelet aggregation may be associated with an increased incidence of cardiac events, but no evidence was identified establishing a relationship between clopidogrel platelet inhibition and bleeding.

In a porcine study, clopidogrel prolonged ear-immersion bleeding time more than did aspirin.[1268] However, no clinical comparison of aspirin and clopidogrel has been performed in surgical patients.

Recommendation

We recommend postponement of elective surgery following coronary stenting (at least 6 to 12 weeks for bare metal stent and one year for drug-eluting stents). **1C**

Kaluza *et al.*[1269] reported that surgery performed within 4 weeks after insertion of a bare metal stent (BMS) is associated with 20% mortality, caused either by ischaemic events following APA interruption or haemorrhagic events while APA therapy was maintained. Other studies confirm that the first month following BMS placement is a high-risk period for non-cardiac surgery. Nuttall *et al.*[1270] reported a postoperative cardiac event rate of 10.5% for surgery within 1 month after stent insertion, versus 3.8% between 1 and 3 months, and 2.8% after 90 days. A global consensus statement recommends

avoidance of non-emergency non-cardiac surgery during the first 4–6 weeks following BMS placement.

Recommendations

We recommend that a multidisciplinary team meeting should decide on the perioperative use of antiplatelet agents in urgent and semi-urgent surgery. **1C**

We suggest that urgent or semi-urgent surgery should be performed under aspirin/clopidogrel or aspirin/prasugrel combination therapy if possible, or at least under aspirin alone. **2C**

Clopidogrel is approved for reduction of atherosclerotic events following recent stroke, recent myocardial infarction or established peripheral arterial disease. The clinical benefit of clopidogrel and aspirin, versus aspirin alone, has been confirmed in patients experiencing percutaneous coronary intervention (PCI) or acute myocardial infarction. The benefit of dual antiplatelet therapy versus aspirin alone in patients with ACS is around one-third of the benefit of aspirin versus no antiplatelet therapy. In the future, prasugrel may be used similarly to clopidogrel, but currently, prasugrel is 'co-administered with acetylsalicylic acid for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI'. A large phase III study (TRITON) compared prasugrel with clopidogrel in 13 608 patients with ACS scheduled to undergo PCI. Prasugrel reduced rates of ischaemic events including stent thrombosis, but increased the risk of major/fatal bleeding.[886]

Drug-eluting stents (DESs) have been associated with stent thromboses at a rate of 1% per year.[1271] Mortality for this complication is 40–50% and the major risk factor for stent thrombosis may be APA withdrawal.[1272] Eisenberg *et al.*[1273] identified 161 cases of late or very late stent thrombosis; 19 cases occurred in patients receiving dual antiplatelet therapy at the time of the event. The median time to event was 7 days if both APAs were stopped simultaneously, 7 days if a thienopyridine was withdrawn first with no ill effect and aspirin subsequently stopped, and 122 days if the thienopyridine was removed but acetylsalicylic acid was maintained. Maintaining APAs throughout the procedure appears to be the safest approach. Among DES patients undergoing non-cardiac surgery, the period of risk for major cardiac events seems to be 1 year.[1274] The incidence of perioperative stent thrombosis remains controversial. Godet *et al.*[1275] reported two stent thromboses in 96 DES patients undergoing non-cardiac surgery, while Schouten *et al.*[1276] observed three late stent thromboses in 99 DES patients undergoing invasive procedures. The risk of stent thrombosis seems to increase over 50-fold during the perioperative period, compared with the annual cumulative risk (0.5–1.5%). Finally, Albaladejo *et al.*[1158] observed major postoperative cardiovascular complications in 10.9% of coronary stent patients undergoing non-cardiac surgery. Preoperative risk factors were anaemia, severe renal failure, urgent surgery, high-risk surgery and interruption of antiplatelet treatment for more than 5 days preoperatively.

The Triton TIMI 38 study showed increased haemorrhagic complications in CABG patients treated with dual antiplatelet therapy including prasugrel, compared with patients treated with clopidogrel.[886]

Recommendation

We suggest that platelet transfusion should be considered (dose: 0.7 x 10^{11} [i.e. two standard concentrates] per 7 kg body weight in adults) in cases of intra- or postoperative bleeding clearly related to clopidogrel or prasugrel. **2C**

No studies of platelet transfusion for reversal of clopidogrel or prasugrel treatment were retrieved.

9.2.3 Ticagrelor

In contrast to the thienopyridines, ticagrelor acts directly on the P2Y12 receptor rather than requiring cytochrome P450 biotransformation. Metabolites of ticagrelor are also active.[1277] Like prasugrel, ticagrelor provides faster (<2 h), greater (approximately 70%) and more consistent P2Y12 inhibition than does clopidogrel (30–40%). Ticagrelor has a rapid onset of action, reversible binding and relatively short duration of action (48–72 h), necessitating twice-daily oral administration. The half-life of the active compound is 12 h. Following cessation, inhibition of platelet aggregation declines to <10% within 4.5 days.[1277]

Recommendations

According to pharmacological characteristics, we suggest that the management of ticagrelor may be comparable to clopidogrel (i.e. withdrawal interval of 5 days). **2C**

Platelet transfusion may be ineffective for treating bleeding clearly related to ticagrelor when given 12 h before. **2C**

The PLATO trial conducted in 18 000 ACS patients showed reduced mortality from vascular causes, myocardial infarction and stroke with ticagrelor compared with clopidogrel.[887] Ticagrelor increased the rate of bleeding unrelated to surgical procedures but did not increase the overall rate of major bleeding.

No studies on efficacy of platelet transfusion in patients treated with ticagrelor were retrieved. When ticagrelor has been administered within the preceding 12 h, its presence in plasma may render platelet transfusion ineffective.

9.3 Anticoagulant agents

9.3.1 Heparin

Heparin is used in clinical practice as unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) and it is necessary to distinguish between the two when making recommendations.

9.3.1.1 Unfractionated heparin

UFH is a heterogeneous mixture of branched glycosaminoglycans; its mean molecular weight is approximately 15 000 Da (range 3000–30 000 Da).[1278] UFH binds antithrombin, forming a complex which inactivates thrombin and coagulation factors Xa, IXa, XIa and XIIa.[1278]

UFH may be administered intravenously or subcutaneously. With intravenous administration, the half-life is >1 h (70–100 min). With subcutaneous administration, the onset of anticoagulation is delayed by approximately 1 h and peak plasma concentrations are reached at 3 h. Clearance occurs via binding to endothelial cells and macrophages, followed by renal metabolism. The process is non-linear and dose-dependent with a half-life after the intravenous administration of a therapeutic dose ranging from 70–100 min.[1278]

Indications for UFH include perioperative thromboprophylaxis (US more than Europe), deep vein thrombosis (DVT) or pulmonary embolism, anticoagulation in CPB (extracorporeal pump) or haemodialysis, coronary pathology (unstable angina, myocardial infarction) and disseminated intravascular coagulation.

Recommendations

We recommend that severe bleeding associated with intravenous UFH should be treated with intravenous protamine at a dose of 1 mg per 100 IU UFH given in the preceding 2–3 h. **1A**

We suggest that severe bleeding associated with subcutaneous UFH unresponsive to intravenous protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of intravenous protamine, with dose guided by aPTT. **2C**

Rapid, effective reversal of UFH can be achieved using intravenous protamine (1 mg protamine neutralises 100 IU of UFH). When UFH has been infused continuously, the dose of protamine should be calculated from the UFH dose administered during the preceding 2–3 h. Protamine can cause hypotension and bradycardia, but slow administration (over 1–3 min) reduces the risks. Protamine is less effective with subcutaneously administered UFH, necessitating continuous and prolonged infusion of protamine.

Activated partial thromboplastin time (aPTT) and/or the plasma concentration of anti-FXa are typically used to monitor the effect of usual therapeutic doses of UFH;[1279] for higher doses (e.g. in cardiac surgery), activated clotting time is the preferred measurement.

9.3.1.2 Low molecular weight heparins

LMWHs are obtained from UFH by chemical or enzymatic depolymerisation. They are widely employed in clinical practice due to their favourable risk/benefit profile, once-daily dosing and reduced requirement for monitoring.

LMWHs include bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, reviparin and tinzaparin. These products differ in molecular weight, pharmacokinetics, anti-FIIa/anti-FXa activity and approved indications, but recommendations apply equally to all LMWHs.[1280]

LMWHs bind to and activate antithrombin. Unlike UFH, not all LMWH molecules can inhibit thrombin (only those with ≥18 saccharides).[1281] The anticoagulant action of LMWH is therefore based mainly on FX inhibition. Unlike UFH, LMWHs have low platelet interaction.

LMWHs have almost 100% bioavailability after subcutaneous administration. Peak plasma concentration is reached approximately 3–4 h after administration and the elimination half-life is around 4–6 h (assuming normal renal function).[1281]

Monitoring the anticoagulant effects of LMWH is usually unnecessary and can be achieved by measuring plasma anti-FXa activity (only necessary in some special cases such as severe renal insufficiency, morbid obese patients or pregnancy).

Recommendations

We suggest that severe bleeding related to subcutaneous LMWH should be treated with intravenous protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered. **2C**

We suggest that severe bleeding associated with subcutaneous LMWH and unresponsive to initial administration of protamine could be treated with a second dose of protamine (0.5 mg per 100 anti-FXa units of LMWH administered). **2C**

Protamine administration does not completely reverse LMWH anticoagulation; although it neutralises anti-FIIa activity, it has limited effects on anti-FXa activity. This is because protamine binds poorly to small LMWH fragments with 8–14 saccharides.[1282] The clinical significance of this is unclear and there are few data describing protamine in LMWH-related human haemorrhage. In clinical practice, protamine (1 mg per 100 anti-FXa units of LMWH administered; conversion of enoxaparin: 40 mg = 4000 international anti-FXa units) is suggested if haemorrhage occurs within 8 h of LMWH administration. A second dose of protamine (0.5 mg per 100 anti-FXa units administered) may be administered if bleeding continues.

9.3.2 Fondaparinux

Fondaparinux is a synthetic analogue of the pentasaccharide sequence found in UFH or LMWH, with selective action against FXa.[1283] It binds to antithrombin and enhances antithrombin inhibition of FXa. Thrombocytopaenia is unlikely to occur in patients receiving fondaparinux.[1284]

Fondaparinux is indicated for preventing venous thromboembolism (VTE), for initial treatment of VTE and for myocardial infarction.

The anti-FXa activity of fondaparinux is higher than that of LMWH. Administered subcutaneously, fondaparinux has an elimination half-life of 17 h in patients without renal impairment (21 h in elderly patients),[1285] allowing once-daily administration. Peak plasma concentration occurs 1.7 h after subcutaneous administration.

Routine coagulation monitoring is not recommended but, as with LMWH, it may occasionally be useful to determine anti-FXa activity (e.g. patients with renal insufficiency).

Recommendation

We suggest that the administration of rFVIIa could be considered to treat severe bleeding associated with subcutaneous administration of fondaparinux (off-label treatment). **2C**

No drug acts as an antidote to fondaparinux. rFVIIa has been proposed to control severe bleeding, but no evidence exists to support this.[1286]

9.3.3 Vitamin K antagonists (VKAs)

VKAs are used in patients with mechanical heart valves, atrial fibrillation or venous thromboembolic disease. Long-acting VKAs are used more commonly than acenocoumarol (Table 2).

Recommendations

We recommend that vitamin K antagonists (VKAs) should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery (mainly anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in VKA-treated patients. **1C**

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score $\leq$2 and patients treated for >3 months for a non-recurrent VTE) undergoing procedures requiring INR < 1.5, VKA should be stopped 5 days before surgery. No bridging is needed. Measure INR on the day before surgery and give 5 mg oral vitamin K if INR exceeds 1.5. **1C**

We recommend bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score >2, patients with recurrent VTE treated for <3 months, patients with a mechanical valve). Day 5: last VKA dose; Day 4: no heparin; Days 3 and 2: therapeutic subcutaneous LMWH twice daily or subcutaneous UFH twice or thrice daily; Day 1: hospitalisation and INR measurement; Day 0: surgery. **1C**

We recommend that for groups 1 and 2 above, VKAs should be restarted during the evening after the procedure. Subcutaneous LMWH should be given postoperatively until the target INR is observed in two measurements. **1C**

We recommend that for group 3 above, heparin (UFH or LMWH) should be resumed 6–48 h after the procedure. VKA can restart when surgical haemostasis is achieved. **1C**

We recommend that in VKA-treated patients undergoing an emergency procedure or developing a bleeding complication, PCC (25 IU FIX kg^{-1}) should be given. **1B**

VKA treatment is monitored by measuring INR.[592,1024] Before surgical intervention, INR should be brought below 1.5. VKA treatment may be interrupted before elective surgery and resumed after surgery (with the first meal). Postoperative heparin is given if the INR is <2. For urgent surgery, PCC (25 IU FIX kg^{-1}) should be given, and additional administration of 5 mg vitamin K1 (intravenous, subcutaneous or oral) is recommended.

9.3.4 Oral inhibitor of activated thrombin

Dabigatran etexilate (Pradaxa, Boehringer Ingelheim, Ingelheim am Rhein, Germany) is the only available oral antithrombin drug, and is licensed throughout Europe for use in orthopaedic surgery. The bioavailability of dabigatran etexilate is 6–8%, its T_{max} is 2 h and its terminal half-life is 14–17 h. Dabigitran is renally eliminated and exhibits no interaction with food.[1284]

Two pivotal orthopaedic surgical studies have shown the efficacy of once-daily oral dabigatran (150 mg or 220 mg) to be as effective as subcutaneous enoxaparin.[1287,1288] Both drugs had similar safety profiles, with no signs of hepatotoxicity. A third study, comparing identical doses of dabigatran and enoxaparin (30 mg twice daily), failed to demonstrate equivalence, because more distal thromboses were observed with dabigatran.[1289] However, rates of proximal thrombosis, major bleeding and symptomatic events did not differ between dabigatran and enoxaparin.

The efficacy of dabigatran has been demonstrated in atrial fibrillation patients; in a large study with a 2-year follow-up, the frequency of primary outcomes (stroke or systemic embolism) was 1.53% per year with 110 mg dabigatran twice-daily and 1.11% per year with 150 mg

Table 2 Vitamin K antagonists

VKA	Molecule	Half-life	Steady state	Initial dose	Duration
Short half-life	Acenocoumarol (Sintrom®)	10 h	2–3 days	4 mg	48–96 h
Long half-life	Fluindione (Previscan®)	30–40 h	3–4 days	20 mg	48–72 h
	Warfarin (Coumadin®)	35–80 h	3–6 days	5 mg	96–120 h
	Phenprocoumone (Marcoumar®)	3–4 days	6 days	6 mg	120–150 h

dabigatran twice-daily compared with 1.69% per year for warfarin.[1290] Relative risk with 110/150 mg dabigatran was 0.91 and 0.66, respectively ($P < 0.001$ for non-inferiority and superiority). Rates of major bleeding were 2.71% per year, 3.11% per year and 3.36% per year with 110 mg dabigatran, 150 mg dabigatran and warfarin, respectively.

Elsewhere, recurrent VTE was observed in 2.4% of patients receiving dabigatran (150 mg twice-daily), compared with 2.1% of patients receiving warfarin.[1291] Similar rates of major bleeding episodes were observed (1.6% vs. 1.9%). Overall, fixed-dose dabigatran was as effective as warfarin, had a similar safety profile and did not require laboratory monitoring.

The lack of biological monitoring with dabigatran could be considered as progress but may also bring insecurity to physicians. A thrombin inhibitor assay (Hemoclot; Aniara, West Chester, OH) is now available to monitor dabigatran therapy.[1292]

No antidote is available for dabigatran etexilate. Dialysis has been shown to be effective to remove dabigatran. Treatments proposed for bleeding include PCC and rFVIIa, but neither has been tested clinically. Van Ryn *et al.*[1292] investigated dabigatran neutralisation using a selective antibody; clinical data are awaited. In emergencies, it may be advisable to wait for two half-lives (34 h) for dabigatran concentrations to reach acceptable concentrations. However, given widely varying interindividual elimination rates, this is merely a fallback solution.

9.3.5 Oral direct factor Xa inhibitors

Several activated factor X (FXa) inhibitors are now marketed or in advanced stages of development.

9.3.5.1 Rivaroxaban

Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin-Wedding, Germany) is an orally active oxazolidone derivative and the first available oral anti-FXa agent. It is a potent anticoagulant with a wide therapeutic window. Rivaroxaban has a bioavailability of 80% and a T_{max} of 2–4 h.[1293] Rivaroxaban inhibits FXa (K_i 0.4 nM) and binds to both free and clot-bound FXa. Two-thirds of rivaroxaban is renally eliminated; its half-life is 9–13 h.

The incidence of thromboembolic events was 49% lower (9.6% vs. 18.9%) in knee arthroplasty patients who received rivaroxaban (10 mg once-daily) compared with 40 mg enoxaparin (RECORD3 study).[1294] An increased bleeding incidence was not observed with rivaroxaban. In the RECORD1 study (35 days of prophylaxis after hip surgery), the primary efficacy outcome occurred in 1.1% of patients who received rivaroxaban compared with 3.7% in the enoxaparin group ($P < 0.001$).[1295] Major VTE occurred in 0.2% of patients receiving rivaroxaban and 2.0% of patients receiving enoxaparin ($P < 0.001$). Major bleeding affected 0.3% of patients receiving rivaroxaban compared with 0.1% receiving enoxaparin ($P = 0.18$), although bleeding at the surgical site was not classified as major bleeding. By integrating the surgical site, it was found that haemorrhage occurred more frequently with rivaroxaban than with enoxaparin.[1296]

A study of high-risk patients with atrial fibrillation (ROCKET-AF trial) used a composite endpoint of all-cause stroke and non-central nervous system systemic embolism.[894] Rivaroxaban 20 mg once-daily, showed comparable benefits to warfarin (2.12% vs. 2.42%; $P < 0.001$ for non-inferiority). Rates of major bleeding were comparable between rivaroxaban and warfarin (3.60% vs. 3.45%; $P = 0.576$). Compared with warfarin, patients receiving rivaroxaban suffered fewer intracranial haemorrhages (0.49% vs. 0.74%; $P = 0.019$), fewer critical organ bleeds (0.82% vs. 1.18%; $P = 0.007$) and fewer bleeding-related deaths (0.24% vs. 0.48%; $P = 0.003$).

Oral rivaroxaban alone (15 mg twice-daily for 3 weeks, then 20 mg once-daily) has been compared with subcutaneous enoxaparin followed by oral VKA (warfarin or acenocoumarol) for 3, 6 or 12 months for the treatment of DVT (EINSTEIN DVT study).[1297] Rivaroxaban displayed non-inferiority in the primary efficacy outcome (36 events [2.1%] vs. 51 events [3.0%] with enoxaparin/VKA; $P < 0.001$). The principal safety outcome occurred in 8.1% of patients in each group.

Safety will remain a concern until high quality data are available. A specific anti-FXa activity test will become available for monitoring rivaroxaban therapy.[897] At the present time, the European Medicines Agency approval limitations should be adhered to.

No antidote to rivaroxaban is available. Proposed therapy for major bleeding includes PCC and rFVIIa. No patient data exists which support this proposal, although PCC effectiveness has been demonstrated in healthy volunteers.[1081] FXa analogues, which could potentially reverse anti-FXa agents, are currently being developed. In emergencies, it may be necessary to wait for two half-lives (14–26 h) to allow rivaroxaban to fall to acceptable concentrations. However, this is merely a fallback solution, given interindividual variability in rivaroxaban elimination rates.

9.3.5.2 Apixaban

Apixaban (Eliquis; Bristol-Myers Squibb, New York, NY) is an oral, reversible, direct FXa inhibitor related to rivaroxaban. Its bioavailability is 51–85%, K_i is 0.08 nM and half-life is 10–15 h.[1293] Elimination of apixaban is both hepatic/biliary (75%) and renal (25%).

In phase III studies, apixaban (2.5 mg twice-daily) was administered following rheumatological surgery. In total knee arthroplasty (ADVANCE-1 study),[1298] the rate of the primary efficacy outcome was 9.0% with apixaban and 8.8% with enoxaparin (30 mg twice-daily). Bleeding incidence was 2.9% with apixaban and 4.3% with enoxaparin

($P = 0.03$). However, apixaban did not meet the non-inferiority criteria because the overall rate of primary events was lower than anticipated.

The ADVANCE-2 study, also in knee replacement surgery, compared apixaban with 40 mg enoxaparin, administered once-daily.[1299] The primary efficacy outcome occurred in 15.1% of patients receiving apixaban and 24.4% receiving enoxaparin ($P < 0.001$). Major VTE occurred in 1.1% of patients treated with apixaban and 2.2% of patients treated with enoxaparin (relative risk 0.50; $P = 0.019$). Clinically relevant bleeding occurred in 3.5% of patients receiving apixaban and 4.8% of patients given enoxaparin ($P = 0.09$). In hip replacement patients (ADVANCE-3 study), the relative risk reduction with apixaban was 64% (1.4% vs. 3.9%, $P < 0.0001$).[1300] Apixaban was also statistically superior to a 40 mg dose of enoxaparin for preventing major VTE (0.45% vs. 1.14%; $P = 0.0054$). Bleeding event rates were similar for both treatment groups.

A large development programme for apixaban is now almost completed. In patients with atrial fibrillation, the AVERROES study[892] was stopped prematurely because apixaban reduced the risk of stroke or systemic embolism by 57% compared with aspirin, with no significant increase in major haemorrhage risk. The ARISTOTLE study[1301] compared apixaban and warfarin in 18 201 patients with atrial fibrillation. The rate of the primary outcome (ischaemic or haemorrhagic stroke, or systemic embolism) was 1.27% per year in the apixaban group, compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% CI, 0.66–0.95; $P = 0.01$ for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60–0.80; $P < 0.001$), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80–0.99; $P = 0.047$).

For biological monitoring, assessment of anti-FXa may be useful (Table 3).

No antidote to apixaban is available. FXa analogues, which could potentially reverse anti-FXa agents, are currently under development. In emergencies, it may be necessary to wait for two half-lives (20–30 h), to allow apixaban to reach acceptable concentrations. Given wide interindividual variability in the elimination rate of apixaban, this is merely a fallback solution.

9.3.5.3 Edoxaban

Edoxaban (Daiichi Sankyo Co., Ltd., Tokyo, Japan) is the third oral anti-FXa agent to be marketed. After oral administration, peak plasma concentrations of edoxaban are achieved within 1–2 h. Terminal elimination half-life for doses of 30–150 mg is typically 8–10 h, with 36–45% eliminated renally.[1293]

Oral edoxaban (15–90 mg once-daily) was compared with subcutaneous dalteparin (5000 IU once-daily) following hip replacement surgery. Both drugs were given for 7–10 days.[1302] Frequencies of VTE were 28.2%, 21.2%, 5.2%, and 10.6% for 15, 30, 60 and 90 mg edoxaban once-daily, respectively (statistically significant dose response, $P < 0.001$), and 43.8% in patients receiving dalteparin ($P < 0.005$). Bleeding incidence was low and comparable between groups.

No antidote to edoxaban is available. FXa analogues, which could potentially reverse the effects of anti Xa agents, are being developed. In emergencies, it may be necessary to wait for two half-lives (10–22 h) to allow edoxaban to reach acceptable concentrations. However, given wide variability in interindividual elimination rates, this is merely a fallback solution.

9.3.6 Management of patients scheduled for a procedure and treated with new oral anticoagulant agents (emergency procedures excluded)

Physicians from outside the field may be unaware of the pharmacological characteristics of many new oral anticoagulant agents (NOAs). A multidisciplinary, international group of physicians (Groupe d'Intérêt en Hémostase Périopératoire) has issued proposals for managing patients treated with NOAs.[1078] As for VKA therapy, three patient groups are considered.

Recommendations

We recommend to assess creatinine clearance in patients receiving NOAs and being scheduled for surgery. **1B**

We suggest that NOAs should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery, (mainly

Table 3 Comparison of new oral antithrombotic agents

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran Etexilate
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Brand name	Xarelto	Eliquis	Lixiana	Pradaxa
Route of administration	Oral	Oral	Oral	Oral
Bioavailability	80%	51–85%	60%	6–8%
T_{max}	2–4 h	3 h	1–3 h	2 h
Half-life	9–13 h	9–14 h	5–11 h	14–17 h
Frequency of administration	Once-daily	Twice-daily	Once-daily	Once- or twice-daily
Renal excretion	66% (half inactive)	25%	36–45%	80%
Antidote	No	No	No	No

anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in NOA-treated patients. **2C**

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score ≤2, patients treated for >3 months for a non-recurrent VTE) undergoing procedures requiring normal coagulation (normal diluted thrombin time or normal specific anti-FXa level), NOAs can be stopped 5 days before surgery. No bridging therapy is needed. **1C**

In patients treated with rivaroxaban, apixaban, edoxaban and in patients treated with dabigatran in which creatinine clearance is higher than 50 ml min^{-1}, we suggest bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score >2, patients with recurrent VTE treated for <3 months). Day −5: last NOA dose; Day −4: no heparin; Day −3: therapeutic dose of LMWH or UFH; Day −2: subcutaneous LMWH or UFH; Day −1: last injection of subcutaneous LMWH (in the morning, i.e. 24 h before the procedure) or subcutaneous UFH twice daily (i.e. last dose 12 h before the procedure), hospitalisation and measurement of diluted thrombin time or specific anti-FXa; Day 0: surgery. **2C**

In patients treated with dabigatran with a creatinine clearance between 30 and 50 ml min^{-1}, we suggest to stop NOAs 5 days before surgery with no bridging therapy. **2C**

We suggest that for groups 2 and 3, heparin (UFH or LMWH) should be restarted 6–72 h after the procedure, taking the bleeding risk into account. NOAs may be resumed when surgical bleeding risk is under control. **2C**

10 PERIOPERATIVE BLEEDING MANAGEMENT IN PATIENTS WITH COMORBIDITIES WITH HAEMOSTATIC DERANGEMENTS AND CONGENITAL BLEEDING DISORDERS

10.1 Patients with comorbidities involving haemostatic derangement

10.1.1 Systemic, metabolic and endocrine diseases

Recommendation

We suggest that patients with haemostatic derangements associated with systemic, metabolic and endocrine diseases should be managed perioperatively in collaboration with a haematologist. **2C**

Systemic, metabolic and endocrine diseases (e.g. amyloidosis, hypothyroidism) are associated with haemostatic derangements. Optimal management strategies for these coagulopathies remain unclear.

Acquired FX deficiency causes the most frequent bleeding manifestations in amyloidosis[1303] and is treated similarly to inherited FX deficiency.

Bleeding diathesis in overt hypothyroidism is mainly due to acquired type 1 VWD.[1304] In a study of patients with thyroid disease, all responded favourably to desmopressin.[1305]

10.1.2 Patients on chronic medication associated with haemostatic derangements

Medications other than antiplatelet and anticoagulant agents (discussed elsewhere in these guidelines – see section 9) may potentially affect haemostasis, including selective serotonin reuptake inhibitors (SSRIs), valproic acid and Ginkgo biloba.

Recommendation

We suggest that SSRI treatment should not be routinely discontinued perioperatively. **2B**

SSRIs have been associated with an increased bleeding tendency, due to serotonin depletion from platelets.[1306] Bleeding frequency appears proportionate to the degree of serotonin reuptake inhibition.

In patients undergoing orthopaedic surgery, intraoperative blood loss increased by 75% among patients using SSRIs, and the risk of blood transfusion almost quadrupled (adjusted odds ratio, 3.71). Patients taking non-serotonergic antidepressants had no increased risk (odds ratio, 0.74).[1307] However, comedications (NSAIDs, methotrexate or iron supplements) also increased transfusion risk.

A study of patients undergoing elective primary total hip arthroplasty reported increased (95 ml or 17%) intraoperative blood loss among SSRI users compared with users of non-serotoninergic antidepressants.[1308] However, transfusion requirements were not increased. Similarly, preoperative SSRI therapy has been shown not to increase allogeneic RBC transfusion during CABG surgery. Adjusted relative risks for transfusion among users of SSRIs, non-selective serotonin reuptake inhibitor antidepressants and other antidepressants were 1.1, 0.9, and 1.0, respectively, compared with patients not using antidepressants.[1309] A retrospective Australian study performed on 4136 patients who underwent CABG surgery also showed that neither SSRI use, nor SSRI and concomitant antiplatelet medication, increased the risk of any bleeding events.[1310] However, in a large cohort study, it has been shown that patients taking an SSRI together with aspirin or dual antiplatelet therapy following acute myocardial infarction were at increased risk of bleeding.[1311]

Therefore, discontinuation of SSRIs before surgery is not recommended.[1312] When used alongside other antiplatelet agents, perioperative use of SSRIs should be individualised.

Recommendation

We suggest individualised perioperative discontinuation of antiepileptic agents, such as valproic acid, which may increase bleeding. **2C**

The antiepileptic drug valproic acid decreases levels of FVII, FVIII, FXIII, platelets, VWF, fibrinogen, protein C

and antithrombin.[1313,1314] However, clinically relevant detriment to haemostasis is uncommon.[1315,1316]

Recommendation

We do not recommend discontinuation of Gingko biloba extracts. **1B**

The effects on blood coagulation have been questioned due to some case reports of spontaneous bleeding after taking Ginkgo preparations. A meta-analysis of 18 randomised controlled trials did not indicate a higher bleeding risk associated with standardised Ginkgo biloba extracts provided as daily oral therapy.[1317]

Ginkgo biloba combined with aspirin also has no impact on coagulation indices.[1318,1319]

10.2 Patients with congenital bleeding disorders

10.2.1 Von Willebrand disease

VWD is the most common hereditary bleeding disorder with an estimated prevalence of 0.6–1.3%.[1320] The disease is caused by deficiency or dysfunction of VWF and is classified into three major categories, which are specifically treated: partial quantitative deficiency (type 1); qualitative deficiency (type 2, with four variants: 2A; 2B; 2M; and 2N); and total deficiency (type 3).[1320,1321] Acquired von Willebrand syndrome comprises defects in VWF concentration, structure or function arising from medical disorders or treatments.[1322]

Bleeding in VWD is due to impaired platelet adhesion and/or reduced levels of FVIII[1320] and is usually mild.[1321]

10.2.1.1 Preoperative evaluation

Recommendations

We suggest that if VWD is suspected preoperatively, the patient should be referred to a haematologist for assessment and planning of the intervention. **2C**

We recommend the use of bleeding assessment tools for predicting the perioperative risk of bleeding. **1C**

Diagnosis of VWD is complex, and no universal approach applies. Initial tests for diagnosing VWD include VWF ristocetin cofactor activity (VWF:RCo), VWF antigen (VWF:Ag) and FVIII coagulant activity (FVIII:C).[1320] Laboratory testing should be guided by history and physical examination.[1323]

Structured questionnaires and bleeding scores are useful for the diagnosis.[1324] A quantitative bleeding assessment tool (BAT) has been evaluated for diagnosing mild bleeding disorders (MBDs).[1325] The positive predictive values in patients referred for haemostatic or familial evaluation were 71.0% and 77.5%, respectively. Bleeding scores ≤ 3 had a high negative predictive value which increased to 99.6% when aPTT measurement was added. Therefore, exclusion of MBDs may be feasible based on BAT and aPTT. In children, the bleeding scores have also limited predictive value for identifying patients with common MBDs but high negative predictive values.[1326,1327]

However, questionnaires can be used to assess bleeding severity of VWD. A mucocutaneous bleeding score (spontaneous, mucocutaneous symptoms) was at least as effective as laboratory testing (circulating levels of VWF and FVIII:C) for predicting bleeding after tooth extraction, and superior to laboratory testing following surgery.[1328] In children with VWD, the median bleeding score has been reported as 7, compared with 0 in controls.[1329] The most frequent clinically significant bleeding symptoms were surgical bleeding, bleeding after tooth extraction and menorrhagia.

10.2.1.2 Perioperative management

Recommendations

We recommend that patients with VWD be managed perioperatively in collaboration with a haematologist. **1C**

Reviews and guidelines covering the management of VWD have been published.[1320,1321,1330,1331] All agree that patients should be managed in specialised centres. However, recommendations for the diagnosis and treatment of VWD are based on observational studies and case series, and are therefore of low grade.

There are three strategies to prevent or control bleeding in VWD: release stored endogenous VWF by stimulating endothelial cells with desmopressin; replace VWF using plasma-derived concentrates; or promote haemostasis with antifibrinolytic drugs or platelet transfusion.

The National Heart, Lung, and Blood Institute guidelines recommend the following:[1320]

1. Treat minor bleedings with desmopressin after a trial performed before clinical use.
2. Use VWF concentrate if the response to desmopressin is inadequate.
3. Administer desmopressin and VWF concentrate based on VWF:RCo and FVIII activity concentrations.
4. For severe bleeding or prophylaxis for major surgery, VWF:RCo and FVIII levels should be 100–200 IU dl^{-1} and 100–250 IU dl^{-1}, respectively.
5. Subsequent dosing should maintain VWF:RCo and FVIII levels above 50 IU dl^{-1} for 7–10 days.
6. For prophylaxis for minor surgery, VWF:RCo and FVIII levels should be >30 IU dl^{-1} (preferably >50 IU dl^{-1}) with maintenance for 1–5 days.
7. For oral surgery in mild–moderate VWD, combined desmopressin and antifibrinolytic drugs should be given.
8. Restrict fluids to maintenance levels in young children and surgical patients receiving desmopressin.

Italian guidelines are similar, except for the lower target and peak concentrations of FVIII recommended for

prophylaxis before major surgery and to be avoided for preventing the risk of thrombosis, respectively.[1330]

Other European centres recommend that guidelines should be stratified for the severity of bleeding, the type of surgery and also for the bleeding score in either VWD type 1, 2 or 3.[1332]

Recommendation
We recommend desmopressin as a first-line treatment for minor bleeding/surgery in patients with VWD, after a trial testing. Treatment regimens are specified by published guidelines. **1C**

Despite a lack of RCTs investigating desmopressin in VWD, desmopressin has been shown to increase plasma VWF and FVIII concentrations from two-fold to more than five-fold over baseline concentrations, with good and excellent results in most surgical adult patients[1333–1336] as well as children.[1337–1339]

The standard desmopressin dose is $0.3\,\mu g\,kg^{-1}$ given intravenously, repeated every 12–24 h.[1320] Response rates are reduced in children <2 years old.[1337]

Desmopressin is usually effective in type 1 VWD; however, not all patients respond to this agent.[1320] In a type 1 VWD cohort ($n = 77$), 83% of patients displayed a complete response to desmopressin; 13% exhibited a partial response and 4% had no response.[1333] Similarly, a 17% risk of bleeding complications after adenotonsillar procedures was reported in children receiving prophylactic desmopressin.[1340] These studies reinforce the importance of a preoperative test infusion of desmopressin.

Desmopressin is variably effective in types 2A, 2N and 2 M VWD, ineffective in type 3 VWD[1330] and controversial in type 2B VWD.[1321]

Tachyphylaxis and hyponatraemia are frequent adverse effects of desmopressin.[1321,1332] Arterial thrombosis has also been reported anecdotally.[1341] Hyponatraemia and seizures have been reported in paediatric cases.[1338]

Recommendation
We recommend replacement of VWF with plasma-derived products for major bleeding/surgery. Treatment regimens are specified by published guidelines. **1C**

VWF can be supplied by cryoprecipitate or human plasma-derived concentrates. Cryoprecipitate is not virus-inactivated and its use is strongly discouraged, except in life-threatening situations when concentrates are not available.[1320]

Plasma-derived VWF concentrates may prevent excessive bleeding in over 90% of VWD patients.[1321] The efficacy has been confirmed in surgical paediatric[1342,1343] and adult patients with VWD.[1336,1343–1350]

For bleeding treatment/prevention in major surgery, a loading dose of $40–60\,U\,kg^{-1}$ is recommended, with $20–40\,U\,kg^{-1}$ every 8–24 h for maintenance.[1320] For minor surgery, the doses are slightly lower, given less frequently and for a shorter duration. Treatment of VWD-related bleeding with VWF concentrates should take account of individual product content and pharmacokinetic data for the relevant disease severity.[1351]

Perioperative monitoring of FVIII:C and VWF:RCo may help determine appropriate dosing.[1320] Depending on VWD type and the concentrate used, PFA-100 might be useful for monitoring the response to FVIII/VWF substitution.[1352]

Adverse reactions to VWF concentrates include allergic and anaphylactic reactions.[1343]

VWF concentrates contain FVIII, and therefore carry a potential thromboembolic risk;[1353] antithrombotic prophylaxis should be considered.[1341]

Recommendation
We suggest that antifibrinolytic drugs should be used as haemostatic adjuncts. Treatment regimens are specified by published guidelines. **2C**

Antifibrinolytic therapy may facilitate effective clotting. Evidence supporting local application of antifibrinolytics is limited, but this treatment has a pharmacodynamic rationale.[1354] Adjuvant local therapy with tranexamic acid added to desmopressin prevented bleeding complications during oral surgery in 84% of VWD patients and reduced the need for factor concentrates.[1334]

For adults, a dose of 4–5 g EACA (oral or intravenous) is recommended, followed by $1\,g\,h^{-1}$ until bleeding is controlled, or for 5–7 days postoperatively.[1321] Tranexamic acid is given intravenously at a dose of at $10\,mg\,kg^{-1}$ every 8–12 h.[1320,1321,1330]

Recommendation
We suggest that platelet transfusion should be used only in case of failure of other treatments. **2C**

When haemorrhage persists despite increased VWF/FVIII levels, administration of platelet concentrate can be helpful.[1355] Platelet concentrates are effective, particularly in patients with type 3 VWD, probably because of their role in transporting VWF to sites of vascular injury.[1321]

10.2.2 Platelet defects

Many classification schemes have been proposed for inherited platelet disorders.[1356,1357] They are uncommon conditions which can alter circulating platelet numbers, function or both. Prominent inherited platelet defects include Glanzmann thrombasthenia (deficiency or functional defect of receptor GPIIb/IIIa) and Bernard-Soulier syndrome (dysfunction or absence of receptor GPIb/IX/V). Both conditions may cause severe bleeding.[1356,1358,1359]

Bleeding with other platelet abnormalities is usually mild/moderate, so they are described as MBDs;[1359]

VWD is included in this category. Typically, they manifest as mucocutaneous bleeding, or bleeding following trauma or invasive surgical or dental procedures.

10.2.2.1 Preoperative evaluation

Recommendations

We suggest referring the patient to a haematologist for assessment and planning of the intervention if inherited platelet defects are suspected preoperatively. **2C**

We recommend the use of bleeding assessment tools for predicting the perioperative risk of bleeding. **1C**

Diagnosis of platelet defects is challenging. Bleeding history is a prerequisite for diagnosing bleeding disorders and should inform the selection of laboratory investigations.[1360] However, MBDs may be undetectable from the bleeding history.[1359] Bleeding scores and quantitative BATs have been proposed for diagnosing MBDs.[1361] Prospective studies found that structured bleeding questionnaires have a high negative predictive value but a low/moderate positive predictive value both in adults[1325] and in children referred for diagnosis.[1327] Measurement of aPTT in addition to a bleeding score significantly increased the diagnostic efficiency for exclusion of patients with suspected MBD in a low-prevalence setting.[1325]

In children, it was shown that questionnaire scores differ among diagnostic groups, giving the potential for stratification of bleeding severity and therefore prediction of bleeding risk during surgical or dental procedures.[1362]

However, no relationship is apparent between bleeding severity and VWF/platelet function variables and the diagnostic efficacy of laboratory testing for hereditary mucocutaneous bleeding was 40.4%.[1363] Therefore, platelet function defects constitute risk factors rather than the unequivocal causes of haemorrhage.

PFA-100 has a high rate of false positive and false negative results and does not predict bleeding risk.[1356] The C-EPI parameter is not sufficiently sensitive to be recommended as a haemostasis screening test,[1364] although it correlates with severity of bleeding history.[1327]

Furthermore, no consensus currently exists regarding the standardisation and interpretation of *in vitro* platelet aggregation/secretion studies for the definitive diagnosis of a platelet defect.

10.2.2.2 Perioperative management

Recommendations

We recommend that patients with severe inherited platelet disorders should be managed perioperatively in collaboration with a haematologist. **1C**

We suggest preoperative haemostatic correction in patients with inherited platelet disorders. **2C**

Most MBDs respond to desmopressin and/or antifibrinolytic drugs, regardless of aetiology.[1359] However, platelet function disorders require specialist management.[1356,1358]

The benefits of prophylactic correction of congenital platelet dysfunction were shown in a prospective study including 72 patients with impaired primary haemostasis.[93] Patients with inherited primary haemostatic impairment (platelet dysfunction including VWD) were preoperatively treated with desmopressin. Most non-responders, defined by persistently abnormal PFA-100 platelet function tests, additionally received tranexamic acid or aprotinin; those with VWD were treated with VWF concentrate, conjugated oestrogens and platelet transfusion. In almost all cases, prophylactic treatment successfully corrected PFA-100 parameters. The frequency of blood transfusion was lower (9.4% vs. 12.2%: $P = 0.202$) in preoperatively treated patients with impaired haemostasis than in patients without impaired haemostasis. In a retrospective group, the frequency of blood transfusion was significantly higher (89.3% vs. 11.3%: $P < 0.001$) in patients without preoperative correction of impaired haemostasis than in patients without impaired haemostasis. Thus, preoperative correction of impaired primary haemostasis appears possible in most patients, and reduces homologous blood transfusions.

Recommendation

We suggest that desmopressin should be used to prevent/control perioperative bleeding in patients with inherited platelet defects. **2C**

The more common, less severe platelet disorders typically respond well to desmopressin, either prophylactically before elective procedures or following trauma.[1357,1365] Desmopressin shortens bleeding time and is therefore assumed to provide clinical benefit.

Most evidence supporting the clinical efficacy of desmopressin in platelet disorders comes from case reports or small case series,[1356] and only one old placebo-controlled study.[1366] The latter study found that desmopressin shortened bleeding time and was sufficient for perioperative management, dependent on the underlying platelet defect. Desmopressin has also been reported as haemostatically effective during obstetric delivery in patients with mild platelet defects.[1367] However, efficacy appears variable, both in mild and in severe platelet defects,[1357] and has rarely been shown in Glanzmann thrombasthenia.[1358]

If desmopressin is contraindicated or is not effective, patients should receive platelet transfusion or possibly rFVIIa.[1356]

Recommendation

We suggest that antifibrinolytic drugs should be used as haemostatic adjuncts in procedures involving patients with inherited platelet defects. **2C**

Antifibrinolytic drugs are useful as adjunctive therapy;[1356,1357] minor bleeding (e.g. dental procedures) may respond to these agents alone.[1358] The use of antifibrinolytic drugs in inherited platelet disorders is not evidence-based. However, tranexamic acid can partially reverse effects of clopidogrel in cardiac surgery.[72]

Recommendation

We recommend that rFVIIa treatment should be considered in patients with Glanzmann thrombasthenia undergoing surgery. **1C**

rFVIIa is licensed for use in Glanzmann thrombasthenia, in which platelet transfusion may be ineffective. Appropriate dosing may be 90 $\mu g\,kg^{-1}$ immediately preoperatively, repeated every 2 h for 12 h, then every 3–4 h until the risk of rebleeding subsides.[1356] An international registry including 59 patients with Glanzmann thrombasthenia showed that rFVIIa was effective in 29/31 surgical procedures and in 77/103 bleeding episodes, eight of which recurred.[1368] Increased success was observed in severe bleeding episodes when a regimen including $\geq$80 $\mu g\,kg^{-1}$ by injection, a dosing interval $\leq$2.5 h and $\geq$3 doses before failure declaration, was used. Patients receiving maintenance doses experienced fewer bleeding recurrences within 48 h than those not receiving maintenance doses. One thromboembolic event and one ureteral blood clot occurred with high-dose rFVIIa. Further thrombotic complications related to rFVIIa therapy have been reported.[1031]

No reliable data exist concerning rFVIIa in bleeding due to platelet dysfunction and the drug is not licensed for other platelet disorders. In one study, rFVIIa was used in children with inherited platelet function disorders: Glanzmann thrombasthenia ($n = 5$); Bernard–Soulier syndrome ($n = 1$); and storage pool disease with severe phenotype ($n = 1$).[1369] Variable results were seen in Glanzmann thrombasthenia, although surgical procedures were successfully covered. Importantly, good/excellent responses were observed in 10/14 bleeding episodes (71%) treated within 12 h, but only 2/11 (18%) treated after 12 h.

In another study, patients with Glanzmann thrombasthenia with bleeding episodes or undergoing dental surgery were treated with antifibrinolytic drugs, with or without additional rFVIIa. In most cases of mild/moderate mucocutaneous bleeding, antifibrinolytic drugs and local measures were considered sufficiently effective, rendering rFVIIa unnecessary.[1370] However, prophylactic administration of rFVIIa was effective in avoiding bleeding during teeth extractions.

Recommendations

We recommend against routine platelet transfusion in patients with inherited platelet disorders. **1C**

There is insufficient evidence to recommend a threshold for perioperative prophylactic platelet transfusion in thrombocytopaenic patients. **C**

Platelet transfusions are appropriate in severe platelet defects and when other options have failed. Due to uncertainty concerning rFVIIa efficacy, platelets are recommended for major elective surgery in patients with Glanzmann thrombasthenia and Bernard–Soulier syndrome.[1356,1365] First doses should be given preoperatively with further doses depending on clinical need. For emergency procedures, random donor platelets may be given, albeit with a high risk of alloimmunisation which can limit future responses.[1365]

Inherited thrombocytopaenias are generally managed similarly to mild platelet disorders.[1371] Thrombocytopaenic patients without evidence of platelet dysfunction should be treated according to platelet count. Platelet transfusion guidelines recommend $\geq$50 000 μl^{-1} for liver biopsy, laparotomy, central line insertion and for major surgery, except ophthalmological and neurological surgery, when $\geq$100 000 μl^{-1} is recommended.[929] Transfusions are usually effective if platelet count is raised above 20 000–30 000 μl^{-1}.

Although guidelines recommend a preoperative platelet transfusion threshold of <50 000 μl^{-1}, supporting evidence is weak.[927] An old study of thrombocytopenic patients with acute leukaemia showed that surgery is safe even in patients with platelet counts <50 000 μl^{-1}, provided that optimal supportive care is available.[1372] Central venous catheters can also be inserted safely in acute leukaemia patients with platelet counts $\geq$20 000 μl^{1} without platelet transfusion, provided that other coagulation abnormalities are absent.[1373]

Recent data suggest also administering fewer platelet transfusions, at lower doses. However, a meta-analysis showed that high-dose platelet transfusion ($3.35–7.7 \times 10^{11}\,l^{-1}$) increased the transfusion interval compared with low-dose platelet transfusion ($2.01–4.6 \times 10^{11}\,l^{-1}$).[1374] The increase in post-transfusion platelet count was also higher in patients receiving the higher dose, with ABO-compatible transfusions. Although bleeding incidence appeared to be independent of platelet count, the above data coming from haemato-oncology should not be extrapolated to inherited thrombocytopaenia.

10.2.3 Haemophilia A and B

Haemophilia A is characterised by reduced plasma FVIII coagulant activity (FVIII:C), and Haemophilia B by FIX deficiency. The prevalence of haemophilia A is 1:10 000, compared with 1:60 000 for haemophilia B.[1375]

Haemophilia patients may develop spontaneous bleeding into joints and bleed excessively after injury or surgery. Clinical severity of the bleeding correlates with the degree of deficiency.[1376] Haemophilia A is classified as mild, moderate or severe, depending on FVIII:C concentration. Mildly affected patients bleed excessively only after trauma or surgery and may have normal routine coagulation test results.[1377]

Factor replacement therapy can induce anti-FVIII or anti-FIX antibodies, known as 'inhibitors'. These are more common in severe forms of haemophilia.[1341] Development of inhibitors in mild haemophilia can change bleeding phenotype from mild to severe.[1377]

Some carrier females have reduced coagulation factor concentrations[1376] and this is important when specific replacement therapy may be required.

Acquired haemophilia is a rare but potentially life-threatening haemorrhagic disorder caused by the development of autoantibodies against FVIII. It may be associated with malignancy, autoimmune disorders, drug reactions and pregnancy.[1378]

Haemophilia therapy involves infusion of coagulation factor concentrates, either prophylactically or during bleeding. Mild haemophilia may be treated with desmopressin and tranexamic acid rather than coagulation factors.[1341]

Recommendations

We recommend that haemophilia patients should be referred preoperatively to a haematologist for assessment/intervention. **1C**

We recommend that surgery in haemophilia patients should be performed in specialised centres with expertise in coagulation disorders. **1C**

With adequate therapy provided in specialised centres, haemophilia patients can safely undergo most surgical procedures.[1379–1382] Retrospective cohort studies found the same outcome after orthopaedic surgery[1382] or general surgery[1381] compared to non-haemophilia controls. General surgical and endoscopic procedures were performed with low morbidity (4% haemorrhagic complications) and mortality rates (1.4%) with appropriate factor replacement and good support from the haemophilia team.[1380] Surgical procedures are also safe in children with haemophilia provided that a standard protocol is followed.[1383]

Recommendations

We recommend adequate perioperative replacement therapy to ensure safe surgery in haemophilia patients. **1C**

We suggest that perioperative replacement therapy (target factor levels and duration) in haemophilia patients follows published guidelines. **2C**

Few reviews of periprocedural replacement therapy have been published, and consensus recommendations are country-specific.[1341,1384–1386] The World Federation of Haemophilia (WFH) recommends that in patients undergoing major surgery, preoperative factor levels should be 80–100%. Postoperatively, factor concentrations should be maintained at 60–80% during days 1 to 3, 40–60% during days 4 to 6 and 30–50% during the second postoperative week. The recommended concentrations for haemophilia B are slightly lower: 60–80%, 40–60%, 30–50%, and 20–40%, respectively.[1387]

An appropriate factor concentration should be maintained for 5–7 days or until wound healing after minor surgery, and for 10–14 days after major surgery. For minor invasive procedures (lumbar puncture, arterial blood gas determination, bronchoscopy with brushings or biopsy, and gastrointestinal endoscopy with biopsy), replacement therapy should only be given before the procedure.[1387]

A literature review and a survey of European practice were published recently.[1379] Although high-quality studies are lacking, replacement therapy appeared efficacious in perioperative management of haemophilia A. The recommendations formulated by the authors are similar to those formulated by the WFH. For liver biopsy, preoperative factor concentrations should be >80% and replacement therapy should continue for ≥3 days. For children undergoing surgery, preoperative factor concentrations should generally be >80% and therapy should be maintained for 7–10 days after tonsillectomy, 3–4 days after circumcision, and ≥3 days after central venous access device insertion.[1379] For dental extractions, treatment with clotting factor concentrate is recommended to obtain a minimum factor concentration of 50%.

The European survey[1379] also demonstrated extensive heterogeneity in clinical practice. However, in most settings there was agreement between published data and clinical practice concerning the intensity and duration of replacement therapy.

Clinical effects of different coagulation factor concentrations have not been investigated, and minimum haemostatic concentrations of individual factors cannot be defined. Only one study showed that lower factor concentrations may be safe in surgical procedures.[1388] Conversely, a high–level clotting factor replacement regimen which maintains the preoperative high concentration for a longer period of time appeared to favour wound healing and to decrease the infection rate in total knee arthroplasty.[1389]

FFP and cryoprecipitate have relatively low clotting factor concentrations and potential viral transmission risks. These products are indicated only if concentrates are not available.[1379,1387]

Recommendation

We recommend either recombinant products or plasma-derived concentrates for perioperative replacement therapy in haemophilia patients. **1C**

Both plasma-derived and recombinant FVIII products proved efficacious for preventing/treating bleeding episodes in haemophilia patients.[1390,1391] Although all plasma-derived coagulation factor concentrates have

excellent safety, UK guidelines recommend recombinant, rather than plasma-derived, products.[1341]

The question of whether plasma-derived or recombinant products are preferable is still under discussion.[1390,1391] It has been suggested that plasma-derived products induce fewer inhibitors than recombinant FVIII.[1391] One study showed that recombinant FVIII carries a 2.5–3-fold higher risk of inhibitor development than plasma–derived FVIII/VFW.[1392] In a paediatric study, increased risk of inhibitor formation was associated with early exposure to recombinant products.[1393] Conversely, another study demonstrated no significant difference in risk of inhibitor development between plasma-derived FVIII and recombinant FVIII.[1394] In addition, the safety and efficacy of recombinant FVIII has been shown in a post-marketing observational study.[1395]

Two systematic reviews reported discordant results.[1396,1397] A prospective cohort study showed that the degree of FVIII purity but not the source of the product influences inhibitor development independently from other risk factors.[1398] In this study there was an increased inhibitor risk with recombinant FVIII and high-purity plasma-derived FVIII compared to low/intermediate-purity plasma-derived FVIII.

In haemophilia B, there is also evidence that both plasma-derived and recombinant products are effective in perioperative management,[1399–1401] providing similar outcomes to those observed among non-haemophiliacs. If recombinant FIX is unavailable, FIX concentrate is preferable to PCC, which carries thrombotic risks.[1341]

Two systematic reviews of thrombotic adverse events[1402] and non-thrombotic, non-inhibitor-associated adverse reactions[1403] to factor FVIII/FIX concentrates used for treatment of haemophilia and VWD confirm these products' high degree of safety. Over a 20 year period, only 20 thrombotic events (2 major and 18 superficial thrombophlebitis) and 12.3% allergic reactions were identified, respectively. No differences were reported between the plasma-derived and recombinant products in the incidence of these events.

Recommendation

We suggest that coagulation factors should be given perioperatively by continuous infusion. **2C**

Continuous infusion of replacement factors may reduce 'wasteful' peaks followed by subtherapeutic concentrations, compared with bolus infusion.[1404] For severe haemophilia A patients undergoing surgery, continuous infusion has been shown to reduce FVIII dosage by 36% compared with bolus infusion, while reducing major bleeding complications to zero (compared with a 17% incidence in patients receiving bolus infusion; $P = 0.06$). The efficacy of continuous infusion has been confirmed in other studies.[1405–1407] The first study designed to obtain regulatory approval for continuous infusion of a FVIII product showed similar surgical bleeding in severe haemophilia patients compared with non-haemophilia control patients.[1408] Increased risk of inhibitor development has been linked with continuous infusion,[1409] but other data do not confirm this risk.[1410]

Continuous infusion is used in nearly half of patients undergoing major orthopaedic surgery, a greater proportion than suggested by the literature[1379]. In a cross–sectional study performed in 22 European centres including 742 patients, continuous infusion was haemostatically very effective (median incidence of postoperative bleeding 1.8%) without increasing the risk of inhibitor development.[1411] Half of the centres aimed to maintain high FVIII levels of $>0.8–1.0\ \mathrm{IU\ ml^{-1}}$ during the early postoperative period, employing an initial infusion rate of $4.0–5.0\ \mathrm{IU\ kg^{-1}\ h^{-1}}$. Despite the high target concentration, the impact of continuous infusion on overall cost was favourable.

Continuous infusion of FIX has also been associated with excellent haemostasis and safety.[1412–1414]

Recommendation

We suggest treatment with either rFVIIa or activated PCCs for haemophilia patients with inhibitors. **2C**

Bleeding in haemophilia patients with inhibitors is usually treated with bypassing agents such as PCC (either activated, which can produce thrombin without any requirement for FVIII, or non-activated) or rFVIIa.[1415,1416] Large quantities of human factor concentrates or porcine products and plasmapheresis are other options to overcome the inhibitors.[1341]

A systematic review found that high-dose FVIII was highly successful (100%) in patients with low-titre, low-responding inhibitors undergoing surgery, although not reliable for high-responding inhibitors.[1417] Porcine FVIII was effective for controlling bleeding in 60–90% of perioperative bleeding in patients with high-titre or high-responding inhibitors. No evidence supported PCC use in surgery, while APCCs controlled approximately 90% of surgical bleeding episodes. rFVIIa controlled 60–100% of surgical bleeding episodes in patients with high-responding inhibitors; results were better when rFVIIa was used early.

In a post-marketing surveillance study of patients with inhibitors, an APCC (FVIII inhibitor bypassing activity [FEIBA]) showed efficacy of 82% and 91% in acute and surgical treatments, respectively.[1035] Additionally, prophylactic treatment improved or stabilised clinical orthopaedic status in 11/13 patients (85%). With a small number of adverse events (<0.04%), FEIBA was judged to be safe. No thrombotic complications were reported. Further studies have since confirmed the efficacy of APCC.[1036,1038,1418–1421]

The dose varied between 50 and $100\ \mathrm{IU\ kg^{-1}}$ given before surgery and thereafter at 6–12-h intervals,

adjusted to an approximate maximum of 200 IU kg^{-1} day^{-1} and tapered when postoperative haemostasis and wound healing permitted. In one study, the median perioperative dose was 130 IU kg^{-1} day^{-1} over 12 days for major surgical procedures and 87.5 IU kg^{-1} day^{-1} over 2 days for minor procedures.[1038] Haemostatic outcome was excellent or good in 78% and 100% of cases, respectively.

In a recent review, good efficacy was reported for rFVIIa in haemophilia patients with inhibitors; rare instances of insufficient haemostasis were attributed to inadequate rFVIIa dosing.[1422] In RCT, a high–dose rFVIIa regimen (bolus dose of 90 μg kg^{-1}, followed by a 90 μg kg^{-1} dose every 2 h for 48 h and then at 4–6 h intervals for 24 h) resulted in fewer postoperative bleeds and fewer extra doses needed than a lower dose regimen (35 μg kg^{-1} at the same hourly intervals).[1423] Recently, a consensus protocol for the use of rFVIIa in orthopaedic surgery in haemophilia patients with inhibitors recommended an initial bolus of 120–180 μg kg^{-1}, followed by a 90 μg kg^{-1} dose every 2 h for 48 h. Thereafter, the intervals may be increased to 3 h for another 48 h; at day 5 after surgery, the intervals may be further increased to 4 h for the next 3 days followed by further lengthening to 6 h until discharge.[987] Adjunctive tranexamic acid is highly recommended.

An updated evaluation of rFVIIa in perioperative bleeding in patients with inhibitors reported an overall effectiveness of 84% and an incidence of thrombotic events of 0.4%.[1424]

The efficacy of continuous infusion of rFVIIa is controversial. In an open-label randomised study, 90 μg kg^{-1} rFVIIa bolus infusion (initially every 2 h) was compared with continuous infusion (initially 50 μg kg^{-1} h^{-1}) in inhibitor-expressing haemophilia A/B patients undergoing surgery.[1425] Haemostatic efficacy was comparable between the groups, with efficacy demonstrated in 8/11 (73%) and 9/12 (75%) subjects in the bolus infusion and continuous infusion groups, respectively. Cumulative 72-h doses were 237.5 and 292.2 mg, respectively. One patient in the bolus infusion group developed venous thrombosis on day 10 after surgery. Better efficacy has been reported by others using rFVIIa continuous infusion.[986,1426,1427] However, most of these patients also received tranexamic acid.

The relative effectiveness of rFVIIa and APCC for the treatment of acute bleeding in haemophilia patients with inhibitors was investigated by a Cochrane review.[1415] Similar haemostatic effects for rFVIIa and APCC were reported, without increasing thromboembolic risk. In the absence of comparative studies carried out in the surgical setting, personal experience, availability and cost may guide the choice of the bypassing agents.[1033]

The use of bypassing agents has a substantial economic impact. rFVIIa appears to be at least cost-neutral relative to APCC for mild/moderate bleeding in this patient population.[1428] In addition, orthopaedic surgery with rFVIIa in haemophilia patients with inhibitors is generally cost-saving, relative to not having surgery.[1429] However, a cost-minimisation analysis for major orthopaedic procedures showed that APCC, alone or alongside rFVIIa, represents a cost-saving approach.[1032]

Some haemophilia patients with inhibitors may become refractory to rFVIIa or APCC therapy. Management of these patients is difficult. In a retrospective review, combined therapy with both agents was described.[1430] Continuous infusion of low-dose rFVIIa (30–70 μg kg^{-1}) and low-dose FEIBA (20–30 U kg^{-1}) appears safe, efficacious and economical in patients refractory to rFVIIa.[1431] However, a critical review of 17 reports regarding parallel use of bypassing agents in the same bleeding episode in 49 patients pointed to an increased risk of thrombosis in these patients.[130]

Potential thromboembolic risks associated with rFVIIa and APCC have been discussed.[1031,1432] However, the methodology of a pharmacovigilance programme suggesting a higher frequency of thrombotic events with rFVIIa over APCC has been criticised.[1031] A review article reported 3.67 thromboembolic events per 100 000 rFVIIa infusions in haemophilia patients,[1433] comparable to figures reported for FEIBA.[1242] Both rFVIIa[1416] and APCC[1242] administration in haemophilia patients with inhibitors is therefore considered safe.

Recommendation

We suggest the use of antifibrinolytic drugs as perioperative adjunct therapy in haemophilia patients. **2C**

In Europe, tranexamic acid is frequently reported as perioperative adjunct therapy in haemophilia patients.[1379] Despite frequent use of tranexamic acid, limited evidence supports its coadministration with FVIII.[1434] A retrospective survey indicated that tranexamic acid used alongside coagulation factor replacement reduces blood loss after orthopaedic surgery compared with coagulation factor substitution alone.[1407] In addition, adjuvant EACA may help to control bleeding in haemophilia patients with inhibitors.[1435]

Antibrinolytic drugs are not recommended for treatment of patients with FIX deficiency already receiving large doses of PCCs.[1387]

The antifibrinolytics are particularly indicated in dental care, where the high fibrinolytic activity of saliva may more easily destabilise the relatively weak clot.[1435] WFH recommends that EACA or tranexamic acid should be started before replacement therapy. The dose of EACA, which should be started the night before or on the morning of the procedure, is 50–100 mg kg^{-1} every 4–6 h for 5–10 days (maximum 24 g per 24 h). The dose for tranexamic acid is 25–50 mg kg^{-1} orally every 6–8 h

for 10 days. A liquid preparation of these drugs may be used as a mouthwash.[1387]

A small double-blind cross-over randomised controlled pilot trial including 16 patients with haemophilia showed that tranexamic acid mouthwash was as effective as factor replacement therapy prior to dental scaling.[1436] Another study including 113 dental extractions in 50 patients with inherited bleeding disorders performed without previous administration of clotting factor concentrates showed that no severe bleeding complications occurred during the follow-up period of 8 days.[1437]

Recommendation

We suggest individualised perioperative thromboprophylaxis in haemophilia patients. **2C**

When perioperative factor substitution is adequate, the risk of venous thrombosis might be considered. A small prospective study including 24 haemophiliac patients undergoing 29 major orthopaedic surgical procedures and screened for VTE by compression ultrasonography showed that subclinical DVT occurred in up to 10% of cases.[1438] No case of clinical DVT or PE was reported. Grade 1 compression above-knee stockings were used in all patients. Based on these findings, routine pharmacological thromboprophylaxis may not be indicated in all haemophiliac patients undergoing major orthopaedic surgery. However, half of the comprehensive haemophilia centres in Europe reported using pharmacological antithrombotic prophylaxis after major orthopaedic surgery[1379] and one centre reported that 82% of haemophiliacs received VTE prophylaxis after the year 2000 with no evidence of increased bleeding complications.[1381] In a study of open heart surgery in haemophilia patients, individualised antithrombotic measures were reported.[1439] Individualised antithrombotic therapy, based on local clinical experience, guidelines for non-haemophilia patients and the patient's clinical characteristics is recommended.[1440]

10.2.4 Rare bleeding disorders

Rare bleeding disorders (RBDs; congenital coagulation factor deficiencies)[1341] have low prevalence: between 1:500 000 and 1:2 000 000.[1365,1441] They account for 3–5% of inherited coagulation disorders,[1442] and FVII deficiency is the most common.

Recommendations

We recommend that patients with rare bleeding disorders should be referred preoperatively to a haematologist for assessment/intervention. **1C**

Bleeding risk in RBD patients is largely assessed using case reports and expert opinion.[1365,1441,1442] Minimum required coagulation factors concentrations are controversial[1443] and correlations between factor concentrations and bleeding risk are generally poor.[1441,1442]

A retrospective survey in patients with hypo- or afibrinogenaemia reported the mean incidence of bleeding episodes in patients receiving prophylaxis to be not much lower than for patients treated on-demand.[1444] Unfortunately, no data were reported describing plasma concentrations of fibrinogen at the time of intracranial bleeding.

Risk of bleeding after surgery in patients with FXI deficiency is particularly high if anatomical sites rich in fibrinolytic activity are involved.[1445] However, among FXI-deficient women giving birth, 69.4% experienced no postpartum haemorrhage, suggesting no relationship between FXI level and risk of postpartum haemorrhage.

Recommendations

We recommend that surgery in patients with rare bleeding disorders should be carried out in consultation with a haematologist with experience in factor deficiencies. **1C**

There is insufficient data to recommend routine perioperative supplementation of deficient factors in patients with rare bleeding disorders. **C**

Perioperative bleeding in patients with RBDs is treated by supplementing the deficient factor.[1446] Coagulation factor supplementation is generally advisable for fibrinogen concentrations $<1\,g\,l^{-1}$ and <20–30% of normal concentrations for other coagulation factors.[1447,1359] Thrombosis is a major concern with coagulation factor supplementation; thrombotic events have been reported following administration of fibrinogen and FXI concentrate.[1365,1441,1442]

The best treatment options, doses and management approaches for patients with RBDs were reviewed in 2004.[1446] Evidence levels were low (descriptive studies and expert opinion). Treatment is generally administered on-demand, so data on preoperative prophylactic therapy are scarce. UK guidelines recommend specific factor concentrates for fibrinogen and FXIII deficiencies.[1341]

An open, uncontrolled, retrospective study showed that fibrinogen concentrate was effective as preoperative prophylaxis.[1448] However, one high-risk patient developed DVT and non-fatal pulmonary embolism; fibrinogen substitution could not be excluded as a contributing factor.

Another open-label, uncontrolled, prospective study of patients with afibrinogenaemia showed that human fibrinogen concentrate can restore haemostasis with a good safety profile.[1234]

Supplementation is not always necessary in FVII deficiency. In a retrospective analysis of surgical procedures performed without replacement therapy in FVII-deficient patients, the median FVII level was 5% and the bleeding rate was 15%.[1449] A threshold level for FVII replacement of 10% was proposed.

FFP (preferably virally inactivated) is the only current option for FV deficiency, and other deficiencies if the

concentrates are not available;[1442] non-virally inactivated cryoprecipitate may be an option for minimising administration volume. PCCs are recommended for FII or FX deficiencies, because specific concentrates are not available. Evidence supporting prophylactic use of PCCs in prothrombin[1450,1451] or FX deficiency is scarce.[1452,1453] rFX and rFXIII are currently being developed. Phase I data suggest that rFXIII may be safe and effective in patients with FXIII deficiency.[1454]

For FXI deficiency, both FXI concentrate and virally inactivated FFP are reasonable, although tranexamic acid alone may suffice for minor procedures.[1341] However, there is evidence that prophylactic treatment is not mandatory in FXI deficiency.[1455]

Vitamin K is the mainstay treatment for vitamin K-dependent clotting factor deficiency.[1456] However, perioperative supplementation using plasma or PCC may also be needed.[1441]

Recommendations

We suggest that rFVIIa should be used in perioperative bleeding due to inherited FVII deficiency. **2C**

If rFVIIa is given to control perioperative bleeding in inherited FVII deficiency, we suggest lower doses than in haemophilia patients. **2C**

There are insufficient data to recommend rFVIIa in perioperative bleeding for patients with other rare bleeding disorders. **C**

rFVIIa is the treatment of choice for FVII deficiency.[1446] If rFVIIa is not available, plasma-derived FVII is favoured over PCC because of PCC's potential thrombogenicity.[1341] A wide rFVIIa dose range (1.2–223.8 $\mu g\,kg^{-1}$) has been reported in FVII deficiency.[1457] Dosing intervals of 2–18 h and treatment durations of 30 h to 2 weeks are described.[1458] Continuous infusion of rFVIIa has also been reported in FVII deficiency.[1459]

The recommended dose of rFVIIa for FVII deficiency is 20–25 $\mu g\,kg^{-1}$ every 4–6 h,[1446] individualised according to bleeding phenotype. In surgery, the specific procedure, tissue/organ involved and type of anaesthesia should be taken into account. Supplementation is recommended until wound healing is established (5–7 days).[1446]

In a prospective study of subjects with FVII deficiency undergoing surgery, rFVIIa ($\geq$3 doses of $\geq$13 $\mu g\,kg^{-1}$) proved effective.[1460] Bleeding occurred in three patients to whom rFVIIa was given at low doses. FVII antibody was observed in one patient undergoing a multiple dental extraction. No thromboses were reported.

Low-dose rFVIIa (33–47 $\mu g\,kg^{-1}$) also appears safe and effective for surgery in patients with severe FXI deficiency and inhibitors.[1461] Co-administration of tranexamic acid has also proved effective,[1462,1463] although it may increase thrombotic risks.

Elsewhere, effective haemostasis was reported in 100% of FXI-deficient patients receiving prophylactic rFVIIa before dental procedures or minor and major operations.[1432] No alternative haemostatic agents or transfusions were administered, except for tranexamic acid. An acute cerebrovascular accident was reported in a patient with a history of cardiovascular disease. The authors concluded that rFVIIa was an effective alternative to plasma-derived FXI, but that rFVIIa may not be suitable for patients with pre-existing thrombotic risk factors.

rFVIIa appears effective in patients with FV or FVIII deficiency and surgical bleeding resistant to supplementation therapy.[1464] Registry data suggest that rFVIIa treatment may control or prevent bleeding in other RBDs, with a favourable safety profile.[1465]

Recommendation

There are insufficient data to recommend periprocedural desmopressin or antifibrinolytic drugs in patients with mild rare bleeding disorders. **C**

Desmopressin has also been used in RBDs, especially mild cases. Limited data suggest a potential role for desmopressin in the treatment of bleeding episodes or prevention of postoperative bleeding in mild FXI defects. Such use is described in a systematic review of 16 case reports.[1466]

Antifibrinolytic agents may be given to patients with RBDs, particularly for mucosal bleeding or bleeding prevention following dental extractions.[1341,1446]

11 FINAL REMARKS

The overall aim of this extensive document is to provide clinicians with evidence-based and up-to-date guidelines for better clinical management of our patients. Great care has been taken by the task force and the steering committee to follow a transparent and comprehensive approach in finding relevant literature and assessing the existing evidence.

Guided by expert assistance, our search strategy was based on predefined criteria and broadly adhered to accepted methodologies, such as those advocated by the Cochrane Collaboration. More than 20 000 abstracts were selected by a sensitive search strategy. As with all database searches, it is possible that some relevant literature was not initially captured. Therefore, to make the process as robust as possible, the authors of each section were asked to conduct supplementary searches and provide the committee with any additional relevant literature. The authors subsequently assessed all publications relevant to their sections.

As initially required by the ESA Scientific and Guideline committee, we applied the SIGN method, which places emphasis on risk of bias when grading the quality of the evidence in publications such as systematic reviews or RCTs. This approach is similar to that advocated by the

Cochrane Collaboration for evaluating the quality of trials and the various domains of bias. When assessing all relevant publications, the authors were required to consider important issues such as publication bias, inconsistency, indirectness, imprecision and funding bias. Finally, the authors were requested to combine the above with their own expert opinions in a transparent manner to generate appropriate and clinically meaningful recommendations.

The team of authors acknowledges that, despite adhering to common assessment tools such as SIGN and GRADE, it is nearly impossible when creating a guideline to avoid an element of subjectivity. Indeed, these guideline tools provide room for subjectivity, for instance when weighing risks versus benefits, considering preferences of patients and evaluating resources and costs. Despite the universal acceptance of its importance, evidence-based medicine is an ideal that is often very difficult to achieve. If guidelines had to be developed using a purely objective approach with no room for subjectivity, we would be left with very little of true value to recommend. Thus, guidelines *per se* will always be subject to a degree of subjectivity. What is essential is that readers are provided with sufficient information to assess the degree of transparency of the process by which a guideline has been developed. We believe that we have achieved this in this detailed document.

It comes as no surprise that there are variations in our practices across Europe. We acknowledge the importance of guidelines as a steering tool but also appreciate the fact that recommendations should be evaluated locally. Some countries and national societies may decide to assess the evidence and recommendations differently.

Some institutions may decide not to introduce devices, medications or strategies advocated in this guideline until further supporting evidence is available. This might be the case with point-of-care testing and products such as fibrinogen concentrate and prothrombin complex concentrate, for which the results of the many ongoing trials are eagerly anticipated.

Furthermore, some institutions may consider it difficult to justify funding the introduction, daily use and maintenance of point-of-care devices, and the higher direct costs of coagulation factor concentrates compared with allogeneic blood products. We note, however, that although allogeneic blood products are perceived as low cost, substantial indirect and infrastructure costs mean that the actual cost of transfusion is high. There is evidence that use of coagulation factor concentrates guided by point-of-care testing may actually reduce costs in some settings. However, cost analyses performed in studies will not reflect the local situation in every hospital and prices for allogeneic blood products and coagulation factor concentrates vary among countries depending on the local market. This task force acknowledges these issues and our recommendations may need to be viewed differently in some countries and institutions until additional evidence to support routine use of these products and devices is published. This statement is in accordance with the official position of the ESA Guideline Committee, and we emphasise that our recommendations can be adopted, modified or not implemented, depending on institutional or national requirements.

Many of the authors and experts involved in developing this guideline have conflicts of interest. Each of these individuals has provided a detailed disclosure statement, as declared in this article. In order to minimise bias in our assessment of the literature, the entire guideline document was subject to internal and external review and was open to critical input from colleagues and national organisations.

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