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GUIDELINES

Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology

First update 2016

Sibylle A. Kozek-Langenecker, Aamer B. Ahmed, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa, Guidrius Barauskas, Edoardo De Robertis, David Faraoni, Daniela C. Filipescu, Dietmar Fries, Thorsten Haas, Matthias Jacob, Marcus D. Lancé, Juan V.L. Pitarch, Susan Mallett, Jens Meier, Zsolt L. Molnar, Niels Rahe-Meyer, Charles M. Samama, Jakob Stensballe, Philippe J.F. Van der Linden, Anne J. Wikkelsø, Patrick Wouters, Piet Wyffels and Kai Zacharowski

The management of perioperative bleeding involves multiple assessments and strategies to ensure appropriate patient care. Initially, it is important to identify those patients with an increased risk of perioperative bleeding. Next, strategies should be employed to correct preoperative anaemia and to stabilise macrocirculation and microcirculation to optimise the patient's tolerance to bleeding. Finally, targeted interventions should be used to reduce intraoperative and postoperative bleeding, and so prevent subsequent morbidity and mortality. The objective of these updated guidelines is to provide healthcare professionals with an overview of the most recent evidence to help ensure improved clinical management of patients. For this update, electronic databases were searched without language restrictions from 2011 or 2012 (depending on the search) until 2015. These searches produced 18 334 articles. All articles were assessed and the existing 2013 guidelines were revised to take account of new evidence. This update includes revisions to existing recommendations with respect to the wording, or changes in the grade of recommendation, and also the addition of new recommendations. The final draft guideline was posted on the European Society of Anaesthesiology website for four weeks for review. All comments were collated and the guidelines were amended as appropriate. This publication reflects the output of this work.

From the Department of Anaesthesiology & Intensive Care, Evangelical Hospital Vienna, Vienna, Austria (SAKL), Department of Anaesthesiology & Intensive Care, Glenfield Hospital, Leicester, United Kingdom (ABA), Department of Anaesthesiology, University Hospital of Copenhagen, Copenhagen, Denmark (AA, JS), Department of Anaesthesiology & Intensive Care, CHU De Grenoble Hôpital, Michallon, Grenoble, France (PA), Department of Anaesthesiology & Intensive Care, Hospital Universitario Rio Hortega, Valladolid, Spain (CA), Department of General Surgery, Lithuanian University of Health Sciences, Kaunas, Lithuania (GB), Department of Anaesthesiology & Intensive Care, University Hospital 'Federico II', Napoli, Italy (EDR), Department of Anaesthesiology, Boston Children's Hospital, Boston, Massachusetts, United States (DFa), Department of Anaesthesiology & Intensive Care, Emergency Institute for Cardiovascular Disease, Bucharest, Romania (DCF), Department of Anaesthesiology, University Hospital of Innsbruck, Innsbruck, Austria (DFr), Department of Anaesthesiology, Children's University Hospital Zurich, Zürich, Switzerland (TH), Department of Anaesthesiology & Intensive Care, Klinikum Straubing, Straubing, Germany (MJ), Department of Anaesthesiology & Pain Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands (MDL), Department of Anaesthesiology & Intensive Care, Hospital Clinico Universitario Valencia, Valencia, Spain (JVLP), Department of Anaesthesia, Royal Free Hospital, London, United Kingdom (SM), Department of Anaesthesiology & Intensive Care, General Hospital Linz, Linz, Austria (JM), Department of Anaesthesiology & Intensive Care, University Hospital of Szeged, Szeged, Hungary (ZLM), Department of Anaesthesiology & Intensive Care, Franziskus Hospital, Bielefeld, Germany (NRM), Department of Anaesthesiology & Intensive Care, Groupe Hospitalier Cochin, Paris, France (CMS), Department of Anaesthesiology, CHU Brugmann, Brussels, Belgium (PJFVDL), Department of Anaesthesiology, Herlev University Hospital, Herlev, Denmark (AJW), Department of Anaesthesiology, Ghent University Hospital, Ghent, Belgium (PWo, PWy) and Department of Anaesthesiology & Intensive Care, University Frankfurt/Main, Frankfurt am Main, Germany (KZ)

Correspondence to Sibylle A. Kozek-Langenecker, Department of Anaesthesiology & Intensive Care, Evangelical Hospital Vienna, Hans-Sachs-Gasse 10-12, 1180 Vienna, Austria; E-mail: sibylle.kozek@aon.at

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1. Summary: recommendations, suggestions and statements

Grade of recommendation shown in bold type (Table 1)

1.1. Evaluation of coagulation status

Before surgery or invasive procedures, we recommend the use of a structured patient interview or standardised questionnaire 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 activated partial thromboplastin time (aPTT), international normalised ratio (INR) and platelet count in elective surgery. **1C**

We recommend the application of intervention algorithms incorporating pre-defined triggers and targets based on viscoelastic haemostatic assay (VHA) coagulation monitoring to guide individualised haemostatic intervention in the case of perioperative bleeding. **1C**

If VHA is not available we recommend the application of intervention algorithms incorporating pre-defined triggers based on conventional coagulation tests. **1C**

1.1.1. Evaluation of platelet function

We suggest preoperative platelet function testing only in association with a positive bleeding history. **2B**

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

Bleeding time is influenced by many variables and is not useful for stratifying bleeding risk. **C**

1.2. Preoperative and postoperative correction of anaemia

Preoperative anaemia in adults and children appears to be a strong predictor for perioperative blood transfusion across various types of conditions and surgeries and may be associated with adverse events. **B**

We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. **1C**

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

We recommend treating iron deficiency with iron supplementation. **1B**

We recommend the use of intravenous iron in preference to oral iron. **1C**

Table 1 Grades of recommendation – Grading of Recommendations Assessment, Development and Evaluation 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.

If other causes of anaemia have been excluded or treated, we suggest erythropoietin-stimulating agents. **2B**

If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. **2C**

In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. **1C**

In non-cancer patients with preoperative anaemia scheduled for elective major surgery, we recommend postponing surgery until anaemia has been corrected. **1C**

In patients who are anaemic following surgery, we suggest the use of intravenous iron. **2C**

1.3. Optimising circulation

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

In cases of uncontrolled bleeding we suggest lower thresholds for cardiac pre-load and/or permissive hypotension may be considered. **2C**

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

We recommend against the use of central venous pressure (CVP) and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimisation of pre-load 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**

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

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

1.3.1. Transfusion triggers

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

Continuous haemoglobin monitoring can be used as a trend monitor. **C**

1.4. Oxygen fraction

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

1.5. Monitoring tissue perfusion

We recommend repeated measurements of a combination of haematocrit (Hct)/haemoglobin, serum lactate, and base deficit 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 (SVV), pulse pressure variation (PPV)], CO_2 gap and central venous oxygen saturation. **1C**

1.5.1. Normovolaemic haemodilution

We suggest the use of acute normovolaemic haemodilution (ANH) in selected settings. **2C**

We recommend against ANH in combination with controlled hypotension. **1B**

In patients with pre-existing or acquired coagulopathy we suggest that the use of ANH is considered carefully. **2C**

1.6. Transfusion of labile blood products

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

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

We recommend pathogen inactivation for fresh frozen plasma (FFP) and 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 a male-only donor policy for plasma-containing blood products to prevent the onset of transfusion-related acute lung injury (TRALI). **1C**

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

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

1.6.1. Storage lesions

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

1.6.2. Cell salvage

We recommend the use of red cell salvage which is helpful for blood conservation in major cardiac and orthopaedic surgery. **1B**

We recommend against the routine use of intraoperative platelet-rich plasmapheresis for blood conservation during cardiac operations using cardiopulmonary bypass (CPB). **1B**

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

We suggest that cell salvage is not contraindicated in cancer surgery, provided that blood aspiration close to the tumour site is avoided and leukodepletion filters are used. **2C**

1.6.3. Plasma and platelet transfusion

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

We recommend early and targeted treatment of coagulation factor deficiencies in the plasma. Sources of coagulation factors are coagulation factor concentrates, cryoprecipitate or high volumes of plasma, depending on the clinical situation, type of bleeding, type of deficiency and resources provided. **1B**

In the treatment of acquired coagulation factor deficiency, we suggest the consideration of a ratio-driven protocol (RBC : plasma : platelet concentrates) early in uncontrolled massive bleeding outside the trauma setting followed by a goal-directed approach as soon as possible. **2C**

We suggest coagulation factor concentrates for the primary treatment of acquired coagulation factor deficiency due to their high efficacy and their minimal infectiousness. **2C**

We recommend against indiscriminate use of plasma transfusion in perioperative bleeding management. **1C**

We suggest platelet concentrate transfusion in bleeding situations clearly related to antiplatelet drugs or thrombocytopaenia less than $50 \times 10^9\ l^{-1}$. **2C**

1.7. General coagulation management

Fibrinogen concentration of less than 1.5 to $2\ g\ l^{-1}$ is considered as hypofibrinogenaemia in acquired coagulopathy and is associated with increased bleeding risk. **C**

We recommend treatment of hypofibrinogenaemia in bleeding patients. **1C**

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

In cases wherein fibrinogen concentrate is not available we suggest cryoprecipitate at an initial dose of 4 to 6 ml kg^{-1}. **2C**

Plasma transfusion alone is not sufficient to correct hypofibrinogenaemia. **C**

In cases of bleeding and low factor XIII activity (e.g. <30%) we suggest administration of factor XIII concentrate (30 IU kg^{-1}). **2C**

In severe perioperative bleeding we recommend that patients on vitamin K antagonists (VKAs) should be given prothrombin complex concentrate (PCC) and intravenous vitamin K before any other coagulation management steps. **1B**

Prolonged INR/prothrombin time (PT) or VHA clotting times alone are not an indication for PCC in bleeding patients not on oral anticoagulant therapy. **C**

We recommend against the prophylactic use of recombinant activated factor VII (rFVIIa) due to increased risk of fatal thrombosis. **1B**

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

We recommend tranexamic acid to prevent bleeding during major surgery and/or treat bleeding due to (or at least suspected) hyperfibrinolysis (e.g. a dose of 20 to $25\ mg\ kg^{-1}$). **1B**

We suggest the use of desmopressin (DDAVP) under specific conditions [acquired von Willebrand syndrome (VWS)]. **2C**

Based on the current literature there is no evidence to recommend antithrombin supplementation in elective surgical patients while they are bleeding.

We recommend structured staff education and training. **1C**

1.7.1. Correction of confounding factors

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

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

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

We recommend that calcium should be administered during massive transfusion if calcium concentration is low, to preserve normocalcaemia (>0.9 mmol l^{-1}). **1B**

We suggest that endovascular embolisation is a well tolerated alternative to open surgical intervention after failed endoscopic treatment for non-variceal upper gastrointestinal bleeding (UGIB). **2C**

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

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

1.7.2. Cost implications

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

Tranexamic acid can reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several major surgical and trauma settings. **B**

We recommend restricting the use of rFVIIa to its licensed indication as, 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 in selected patients. **A**

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

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

1.8. Algorithms in specific clinical fields

1.8.1. Cardiovascular surgery

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

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

We recommend prophylactic administration of tranexamic acid before CPB in patients undergoing coronary artery bypass grafting (CABG) surgery. **1A**

We suggest tranexamic acid can be applied topically to the chest cavity to reduce postoperative blood loss following cardiac surgery. **2C**

In complex cardiovascular surgery we recommend fibrinogen concentrate infusion guided by VHA monitoring to reduce perioperative blood loss. **1B**

We suggest that rFVIIa may be considered for patients with intractable bleeding during and after 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 recommend the use of standardised VHA-guided haemostatic algorithms with pre-defined intervention triggers. **1B**

1.8.2. Gynaecological (non-pregnant) surgery

We suggest that normovolaemic haemodilution should not be used as it does not reduce allogeneic transfusion. **2B**

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

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

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

Tranexamic acid may reduce perioperative bleeding in gynaecological cancer surgery. **C**

1.8.3. Obstetric bleeding

We recommend that peripartum haemorrhage (PPH) should be managed by a multidisciplinary team. **1C**

We recommended the use of an escalating PPH management protocol including uterotonic drugs, surgical and/or endovascular interventions and procoagulant drugs. **1B**

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

We suggest that patients with known placenta accreta be 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**

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

We suggest assessing fibrinogen levels in parturients with bleeding, as levels less than 2 g l^{-1} may identify those at risk of severe PPH. **2B**

Dynamic platelet count decrease or a level less than 100×10^9 l^{-1} at the onset of labour, particularly if combined with plasma fibrinogen level less than 2.9 g l^{-1}, may indicate an increased risk of PPH. **C**

At the beginning of labour aPTT and PT are of little predictive value for PPH. **C**

VHA can identify obstetric coagulopathy. **B**

We recommend against pre-emptive fibrinogen replacement; however, in ongoing PPH with hypofibrinogenaemia we recommend fibrinogen replacement. **1C**

In severe PPH we suggest a VHA-guided intervention protocol. **2C**

We suggest that tranexamic acid be considered before caesarean section and in cases of antepartum bleeding. **2B**

We recommend the administration of tranexamic acid in PPH at a dose of 1 g intravenously (IV) as soon as possible, which can be repeated if bleeding continues. **1B**

1.8.4. Orthopaedic surgery and neurosurgery

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

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

1.8.5. Paediatric surgery

We suggest low-volume sampling for standard coagulation tests and VHA-guided interventions. **2C**

We recommend the use of isotonic and balanced resuscitation fluids in bleeding children. **1C**

Except for premature babies and cyanotic newborns, haemoglobin targets in bleeding children are 7 to 9 g dl^{-1}. **C**

1.8.6. Visceral and transplant surgery

Despite PT, aPTT and INR indicating coagulopathy in chronic liver disease (CLD), global coagulation tests (thrombin generation and VHA) 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 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 transplant (OLT). **C**

We recommend a low CVP and restrictive fluid administration during liver surgery to reduce bleeding. **1B**

We recommend tranexamic acid for treatment of fibrinolysis (evident from microvascular oozing or VHA clot lysis measurement) but not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis postreperfusion. **1C**

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

1.8.7. 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**

Transjugular intrahepatic portosystemic stent-shunt (TIPSS) can be suggested as an option for rescue therapy after initial medical and endoscopic therapy fail. **2B**

We recommend early interventional endoscopy and the immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding. **1B**

Tranexamic acid reduces mortality but not re-bleeding. **B**

1.8.8. 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 DDAVP should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. **2C**

1.9. Antithrombotic drugs

1.9.1. Antiplatelet agents

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

Where aspirin withdrawal before surgery is considered, we recommend a time interval of 3 days. **1C**

In patients with risk factors for vascular complications naïve of any antiplatelet treatment, it is not recommended that treatment with aspirin be initiated preoperatively. **1B**

In patients treated chronically with aspirin for the secondary prevention of cardiovascular events, except those patients with coronary stents, we recommend aspirin interruption for procedures where there is a very high bleeding risk. **1B**

In patients chronically treated with aspirin for secondary prevention of cardiovascular events, we recommend aspirin be maintained during and after low and medium bleeding risk procedures. **1B**

We suggest careful consideration of postoperative bleeding complications when timing the first postoperative administration and dose of anticoagulants along with resumption of aspirin. **2C**

For intraoperative or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7×10^{11} per 10 kg body weight in adults). **2C**

We recommend that aspirin be continued for at least 4 weeks after bare metal stent (BMS) implantation and 3 to 12 months after drug-eluting stent (DES) implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high. **1A**

We suggest that P2Y12 inhibitor treatment be considered for at least 4 weeks after BMS implantation and 3 to 12 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high. **2A**

If clinically feasible, we suggest postponing (semi-urgent) surgery for at least 5 days after cessation of ticagrelor and clopidogrel, and for 7 days in the case of prasugrel, unless the patient is at high risk of an ischaemic event. **2B**

We recommend that antiplatelet agent (APA) 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 that a multidisciplinary team meeting should decide on the perioperative use of APAs 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 be considered (dose: 0.7×10^{11} per 10 kg body weight in adults) in cases of intraoperative 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 transfusions may be ineffective for treating bleeding related to ticagrelor if given within 12 h of the drug's administration. **C**

1.9.2. 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 to 3 h. **1A**

We suggest that severe bleeding associated with subcutaneous (SC) 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 the dose guided by aPTT. **2C**

We suggest that severe bleeding related to SC low molecular weight heparin (LMWH) should be treated with intravenous protamine at a dose of 1 mg per 100 antifactor Xa units of LMWH administered and, if unresponsive, with a further 0.5 mg protamine per 100 antifactor Xa units. **2C**

1.9.3. Fondaparinux

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

1.9.4. Vitamin K antagonists

We recommend that VKAs should not be interrupted in patients undergoing low bleeding risk procedures: skin surgery, dental and oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomies), nor for most ophthalmologic surgery [i.e. mainly anterior chamber (cataract)]. **1C**

We recommend that for low or moderate thrombotic risk patients [e.g. atrial fibrillation patients with $CHADS_2$ score ≤ 4; patients treated for >3 months for a non-recurrent venous thromboembolism (VTE)] undergoing procedures requiring INR less than 1.5, VKA should be stopped 3 to 5 days before surgery (acenocoumarol, warfarin). 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 thrombotic risk patients (e.g. atrial fibrillation patients with a $CHADS_2$ score >4; patients with recurrent VTE treated for less than 3 months; patients with a prosthetic cardiac valve). Warfarin: last dose 5 days before surgery; 4 days before surgery, no heparin; 3, 2 and 1 day before surgery, LMWH (last dose 24 h before surgery) or SC UFH twice or thrice daily; day 0, surgery. Acenocoumarol: 3 days before surgery, last dose; 2 and 1 day before surgery, same protocol as for warfarin. **1C**

We suggest that the therapeutic dose of LMWH or UFH should be tailored for each patient, depending on the respective thrombotic and bleeding risks. **2C**

We recommend that for low bleeding risk patients, VKAs should be restarted during the evening or the day after the procedure (at least 6 h after). Therapeutic doses of

LMWH should be given postoperatively until the target INR is observed in two following measurements. **1C**

We recommend that for moderate to high thrombotic risk patients, prophylactic doses of heparin (UFH or LMWH) should be started during the evening or the day after the procedure (at least 6 h after) and given for up to 48 to 72 h, and then therapeutic anticoagulation should be resumed. VKA can restart at that time or later, only when surgical haemostasis is achieved. **1C**

In VKA-treated patients undergoing an emergency procedure, we recommend that INR must be measured on the patient's admission to the hospital, with the administration of four-factor PCC to reverse VKA anticoagulant effects (e.g. at an initial dose of 25 IU factor IX kg^{-1} at an INR of 4) rather than the transfusion of plasma. **1B**

In bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the administration of four-factor PCC 25 to 50 IU factor IX kg^{-1} plus 5 to 10 mg IV vitamin K. **1B**

If PCC is not available, then in bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the transfusion of plasma (15 to 20 ml kg^{-1} plus 5 to 10 mg IV vitamin K). **1C**

1.9.5. Direct oral anticoagulants

We recommend assessment of creatinine clearance in patients receiving direct oral anticoagulants (DOACs) who are scheduled for surgery. **1B**

We suggest that DOACs should only be withheld the day before surgery for patients undergoing low bleeding risk procedures such as skin surgery, dental and oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but no polypectomies) and most ophthalmological surgery. **2C**

For intermediate and high bleeding risk procedures

(1) we recommend that rivaroxaban, apixaban and edoxaban should not be given for 2 days before the procedure (i.e. last oral intake 3 days before), pending a creatinine clearance (Cockcroft–Gault formula) above 30 ml min^{-1}. No bridging therapy is needed. **1C**
(2) we recommend that dabigatran should not be given for 3 days before the procedure (i.e. last oral intake 4 days before), if the creatinine clearance is above 50 ml min^{-1} and 4 days before the procedure (i.e. last oral intake 5 days before), if the creatinine clearance is between 30 and 50 ml min^{-1}. No bridging therapy is needed. **1C**

We suggest that in severe bleeding patients treated with dabigatran, a specific antidote (idarucizumab) should be considered. **2C**

We suggest that for low bleeding risk procedures, when haemostasis is achieved, DOACs should be recommenced during the evening after the procedure (at least 6 h after). **2C**

We suggest that for intermediate and high bleeding risk procedures, prophylactic doses of LMWH or DOACs (according to specific indications) should be given postoperatively whenever VTE prophylaxis is requested and then the full therapeutic dose of DOAC should be resumed up to 72 h postoperatively, when surgical haemostasis is achieved. **2C**

1.10. Comorbidities involving haemostatic derangement

1.10.1. Systemic, metabolic and endocrine diseases

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 individualised preoperative discontinuation of selective serotonin reuptake inhibitor (SSRI) treatment. **2B**

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

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

1.11. Patients with congenital bleeding disorders

1.11.1. Preoperative assessment

We suggest referring the patient to a haematologist for assessment and planning of the intervention if inherited bleeding disorders (IBDs) are suspected preoperatively. **2C**

We recommend the use of bleeding assessment tools (BATs) for detecting and predicting the perioperative risk of bleeding before surgery and invasive procedures. **1C**

1.11.2. General perioperative management

Surgery can be safely performed in patients with IBDs when there is appropriate careful preoperative planning, appropriate replacement/substitution therapy, and multidisciplinary team management. **C**

We recommend that patients with IBDs be managed perioperatively in collaboration with a haematologist, preferably in dedicated centres with expertise in coagulation disorders. **1C**

We suggest preoperative haemostatic correction in patients with IBDs depending on the type of surgery. **2C**

1.11.3. Von Willebrand disease

We recommend DDAVP as a first-line treatment for minor bleeding/surgery in patients with von Willebrand disease (VWD), after a trial testing. The standard

regimen is 0.3 $\mu g\,kg^{-1}$ dissolved in 50 ml saline and infused IV over 20 to 30 min, repeated every 12 to 24 h usually for no more than 3 days. **1C**

We recommend replacement of von Willebrand factor (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**

1.11.4. Platelet defects

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

We suggest that 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**

1.11.5. Haemophilia A and B

We recommend adequate perioperative replacement therapy to ensure well tolerated 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 DDAVP as first-line perioperative therapy in patients with mild haemophilia A as long as factor VIII can be raised to an appropriate therapeutic level. **2C**

1.11.6. Rare bleeding disorders

There are insufficient data to recommend routine perioperative supplementation of deficient factors in patients with rare bleeding disorders (RBDs).

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

If rFVIIa is given to control perioperative bleeding in inherited factor VII deficiency, we suggest lower doses (e.g. 20 to 25 $\mu g\,kg^{-1}$ every 4 to 6 h) than in haemophilia patients with inhibitors. **2C**

There are insufficient data to recommend rFVIIa in perioperative bleeding for patients with other RBDs.

There are insufficient data to recommend periprocedural DDAVP or antifibrinolytic drugs in patients with mild RBDs.

2. Introduction

Perioperative bleeding management is a complex and changing field requiring multiple assessments and appropriate strategies to optimise patient care. There is an ongoing drive to find new alternatives to transfusion, a desire to reduce unnecessary use of blood products and a focus towards more evidence-based perioperative practice. In this dynamic area of medicine it is imperative to provide healthcare professionals with clinically useful and up-to-date data concerning the diagnosis and treatment of patients with perioperative bleeding. As such, the European Society of Anaesthesiology (ESA) strongly supports the development of high-quality, evidence-based clinical practice guidelines to help standardise the approach to patient care and to improve overall clinical practice.[1]

In 2013, the ESA developed an extensive set of evidence-based guidelines[2] for the management of severe perioperative bleeding with the overall aim of providing an up-to-date review and synthesis of the evidence and recommendations to help guide clinicians towards safer and more cost-effective strategies for minimising severe perioperative bleeding and thus maximising blood conservation. The current guidelines update provides additional information to assist the clinician to PREPARE, PLAN and take ACTION. PREPARE for any potential bleeding risks by performing preoperative assessments, particularly to detect anaemia and allow time for its correction. PLAN for any intraoperative bleeding that may occur by utilising transfusion algorithms that incorporate pre-defined transfusion triggers to help guide haemostatic intervention, by being aware of the limitations of standard coagulation tests and by modifying the approach accordingly to use point-of-care testing and others. If potential bleeding risks are known in advance and a plan of treatment is in place, the necessary ACTION can be set in motion as required. Because of the increasing evidence in this field, an update of the guidelines was planned every 2 years.

This document not only details the retained recommendations, suggestions and statements from the original guidelines published in 2013[2] but also includes new recommendations as well as revisions to the wording and grades of some of the original recommendations. Additional clinical questions have been included in the update.

3. Methods

3.1. Task force selection

In the planned process of revising the guideline, 'Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology' published in 2013,[2] the ESA Guideline Committee (Chairman, EDR) re-nominated the ESA Task Force previously selected, chaired by SAKL, and composed of AA, PWo, CA, and EDR. The ESA Guideline Committee and the task force defined the scope of the guideline revision, which prompted the core group to invite scientific societies involved in the field to suggest experts to join the task force as affiliate co-authors (advisory group). The first meeting of the extended panel was held during the Euroanaesthesia meeting in Berlin in May 2015.

3.2. Search for evidence

For this update we searched Medline (Ovid), Embase (Embase.com), the Cochrane Library (Wiley), BIOSIS (Web of Science), Science Citation Index Expanded (Web of Science), Conference Proceedings Citation Index – Science (Web of Science), and PubMed (for non-Medline contents). The searches were conducted between March and July 2015 and limited to publication dates since 2011 or 2012 (depending on the search). Guidelines, case reports, editorials and commentaries were excluded from the search result. No other limitations were used. As with the original guidelines, we conducted 12 separate searches, using both free text terms and subject headings: one general search on the topic of perioperative bleeding, one search for systematic reviews, and one search for each topic within these guidelines. A total of 18 334 references were retrieved. The exact search strategies and numbers of references for each search are reported in Appendix 1 (Supplemental Digital File: ESA POB guidelines update search Nov2016.docx, http://links.lww.com/EJA/A118). Both task force members and the extended panel members reviewed the selected articles relevant to their sections and evaluated these according to the ESA policy on guidelines development.[1] A total of 733 references were included for the guideline update.

3.3. Guideline preparation

To revise the guidelines, the task force referred to the same series of key clinical questions about the management of severe perioperative bleeding as used for the previous guideline. These questions formed the basis for reviewing the evidence published after 2012 and, when the new evidence was strong enough, for developing new recommendations or modifying the existing recommendations. Downgrading of the quality of evidence occurred for some existing recommendations; this was due to methodological issues in the studies and not because of new contradictory evidence. All downgraded recommendations are still valid and should be considered as clinically relevant.

Guidance in the clinical fields of anaemia management, optimisation of haemostasis, and blood conservation modalities makes these ESA guidelines the first European guidelines on patient blood management (PBM). The World Health Organization encouraged all member states to implement PBM programmes employing such multiple combined strategies to increase and preserve autologous erythrocyte volume to minimise the transfusion of blood components such as RBCs, platelets, FFP.[3] Anaemia is associated with increased morbidity and mortality and may also be a condition that prompts medical professionals to initiate RBC transfusion.[4] The latter itself may be associated with increased morbidity due to infectious, immunological or pulmonary complications.[5–8] These complications are also recorded following the administration of platelets and/or FFP.[8]

General guidance on the management of severe perioperative bleeding is applicable across all clinical settings. Therefore, to reduce redundancy, the section on general coagulation management is relevant to all patient categories whereas guidelines that are specific to a particular setting are detailed in separate sections. Any guidance for therapeutic interventions is always based on the prerequisite of severe bleeding manifestations: in the absence of bleeding the correction of a laboratory result indicating a pathological coagulation parameter is not recommended.

The final draft of the guideline was reviewed by external reviewers and posted on the ESA website for four weeks, and all individual and national ESA members were invited to comment. The final manuscript was approved by the Guidelines Committee and the ESA Board before submission for publication.

The overall aim of these updated guidelines is to provide healthcare professionals with the most recent evidence to help ensure improved clinical management of patients with perioperative bleeding. The search strategy was based on pre-defined criteria, and supplementary searches were performed to make this process as robust as possible. The authors assessed all publications relevant to their sections and the existing 2013 recommendations were revised with respect to wording or changes to the grading of the quality of evidence, as appropriate. New recommendations were also prepared to reflect additional clinical questions.

The guideline uses the same grading system as in the previous guidelines – the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[2] (Table 1). Therefore, 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). Statements are

accompanied only by a letter, to indicate the quality of the evidence supporting the statement.

It is important to emphasise that these recommendations can be adopted, modified, or not implemented, depending on the requirements of different institutions or countries.

4. Evaluation of coagulation status

4.1. Perioperative coagulation testing

New evidence supports the existing recommendations and this is detailed below for the relevant sections.

4.1.1. Standard laboratory tests for coagulation monitoring

4.1.1.1. Fibrinogen concentration

Fibrinogen concentration is often determined indirectly using the Clauss method.[9] In a recent paper, considerable differences were found between Clauss-based plasma fibrinogen measured using different detection methods.[10] However, the similarity between measurements, shortly before weaning from CPB and after CPB within the same centres, indicated that on-pump measurements could provide an early estimation of fibrinogen deficit after CPB.

Fibrinogen levels may be linked with postoperative blood loss and a recent systematic review reports a significant but weak-to-moderate correlation between preoperative and postoperative fibrinogen levels and postoperative blood loss in cardiac surgery.[11]

4.1.2. Viscoelastic haemostatic assay coagulation monitoring

VHA coagulation monitoring uses whole blood and is performed in the emergency room, operating theatre, or the central laboratory. In a recent systematic review, VHA coagulation monitoring was found to be cost-saving and more effective than standard laboratory tests (SLTs), in both patients undergoing cardiac surgery and trauma patients.[12]

4.1.2.1. Commonly used blood modification agents for viscoelastic haemostatic assay coagulation monitoring

VHA coagulation monitoring can be performed using recalcified, citrated blood alone [native thromboelastometry (NATEM) assay with no activation enhancement or additional modifications, and clotting is 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 the observed coagulopathy. The most commonly used VHAs to measure fibrin clot quality include the functional fibrinogen and FIBTEM (Fibrinogen thromboelastometry) assays. These assays measure the strength of the fibrin-based clot and a low functional fibrinogen/FIBTEM clot strength usually indicates fibrinogen deficiency. In a study by Erdoes *et al.* [13] the authors concluded that, when measured on CPB prior to weaning, a FIBTEM A10 (clot amplitude at 10 min) 10 mm or less may be an early alert for post-CPB fibrinogen levels below, or within, the range for supplementation (1.5 to 2.0 g l^{-1}) recommended in case of post-CPB coagulopathic bleeding.

There are indications that EXTEM (extrinsic thromboelastometry), INTEM (intrinsic thromboelastometry) and APTEM (aprotinin thromboelastometry) are associated with fibrinogen and platelet levels: INTEM clotting time (CT) correlated significantly with aPTT and FIBTEM correlated significantly with fibrinogen, whereas factor VIII (FVIII) correlated significantly with all ROTEM (rotational thromboelastometry) parameters except EXTEM CT, INTEM CT, FIBTEM CT and APTEM clot formation time (CFT) and maximum clot firmness (MCF).[14] However, other publications have found it difficult to find a clear correlation between findings from VHA [TEG (thromboelastography) and ROTEM] monitoring to SLTs such as PT and aPTT perioperatively and overall haemostatic measurement.[15–17]

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

4.1.3.1. Standardised bleeding history and clinical evaluation

Recommendations

Before surgery or invasive procedures, we recommend the use of a structured patient interview or standardised questionnaire 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, INR and platelet count in elective surgery. **1C**

Structured patient interviews are a primary tool for preoperative assessment of bleeding risk, and physical examination should focus on signs of bleeding or diseases which may cause haemostatic failure. Comorbidities, including renal dysfunction, are independent risk factors for bleeding and transfusion; for example, a recent systematic review found that chronic kidney disease is associated with perioperative bleeding but not bleeding that required reoperation.[18] Among cardiac surgery patients, patient-related predictors of excessive bleeding after surgery were reported to be male gender, higher preoperative haemoglobin levels, lower BMI, diabetes mellitus, impaired left ventricular function, lower amount of pre-bypass thrombin generation, lower preoperative platelet counts, decreased preoperative platelet aggregation, preoperative platelet inhibition level more than 20%, preoperative thrombocytopaenia, and lower preoperative fibrinogen concentration.[19]

4.1.3.2. Preoperative use of standard laboratory tests

Preoperative use of SLTs is not recommended by current ESA guidelines. Furthermore, in patients without a previous history of bleeding or bleeding disorders, SLTs are not generally recommended.[20] In the neurosurgical setting, the value of preoperative PT testing is limited in patients awaiting elective procedures in whom a normal bleeding history can be established.[21]

A recent meta-analysis reported a significant but weak-to-moderate correlation between preoperative and postoperative fibrinogen levels and postoperative blood loss in cardiac surgery.[11] Preoperative measurement of fibrinogen may be useful to identify those patients at risk of postoperative bleeding.

Recent evidence indicates that patients with end-stage liver disease and an elevated INR can safely undergo invasive cardiac procedures as elevated INR does not predict catheterisation-related bleeding complications.[22] However, in paediatric living donor liver transplantation, preoperative INR was the only predictive risk factor for massive blood transfusion.[23] In adult OLT recipients, a higher preoperative INR was also found to be associated with increased RBC administration (both autologous and cell salvage). Each INR increase of 1 unit resulted in a 36% increase in the predicted number of units of RBCs required.[24] However, there is currently little evidence to support additional, routine application of point-of-care INR testing in the preoperative setting to predict bleeding tendency. For example, point-of-care INR measurements for trauma patients during various stages of admission and resuscitation could not be used to identify or exclude patients with acute traumatic coagulopathy.[25]

4.1.3.3. Preoperative use of viscoelastic haemostatic assay coagulation monitoring

VHA is used for rapid diagnosis of bleeding causes and is of most value intraoperatively. Indiscriminate preoperative coagulation monitoring using VHAs is unlikely to be cost-effective, but it may be warranted in combination with SLTs in patients with bleeding disorders such as VWD, factor XIII (FXIII) deficiency, and haemophilia A with dysfibrinogenaemia, or in patients with preoperative anticoagulant treatment.[26,27]

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

4.1.4.1. Intraoperative use of standard laboratory tests

For laboratory measurement of fibrinogen to be useful in cardiovascular surgery, analysis would need to begin before the patient is taken off CPB. Such measurement is prevented by the sensitivity of the Clauss assay to heparin. However, a study by Solomon *et al.*[10] demonstrated that there were no significant differences in fibrinogen concentration before and after weaning from CPB, for most centres and methods used. The similarity between measurements shortly before weaning from CPB and after weaning suggests that on-pump measurements could provide an early estimation of a likely deficit in fibrinogen post-CPB, and therefore guidance for any haemostatic therapy. In paediatric non-cardiac surgery patients, SLTs correlate poorly with intraoperative activated clotting time (ACT).[28]

4.1.4.2. Intraoperative use of viscoelastic haemostatic assay coagulation monitoring

A recent health technology assessment reports findings from a meta-analysis showing that perioperative VHA monitoring is associated with a reduced need for transfusion of RBCs, platelets and FFP compared with monitoring by SLTs.[12] If using VHA coagulation monitoring, appropriate transfusion triggers should be considered carefully.[29]

4.1.4.2.1. Intraoperative viscoelastic haemostatic assay monitoring in trauma

In paediatric patients with traumatic brain injury, hypocoagulation measured by TEG is associated with mortality and hypercoagulation is associated with survival.[30] The timing of sampling and pre-hospital haemostatic assessment was investigated in a prospective study of 50 trauma patients and no additional information was gained by pre-hospital assessment.[31] A small randomised controlled trial (RCT) of 30 patients with surgical excision of burn wounds performed on the third day after burn trauma showed a reduced need for allogeneic blood transfusions when a bleeding management algorithm based on thromboelastometry was used.[32] A recent Cochrane systematic review investigating the diagnostic test accuracy of TEG and ROTEM in patients with clinically suspected trauma-induced coagulopathy found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM: this was due to the small number of included studies and concerns about the risk of bias.[33] These results are supported by other studies.[34,35]

4.1.4.2.2. Intraoperative viscoelastic haemostatic assay monitoring in cardiovascular surgery

The value of VHA monitoring to guide haemostatic therapy following CPB has been demonstrated in several RCTs.[36–46] The majority of published randomised trials investigating VHA-guided transfusion have been performed in cardiac surgery and several reviews have reported a reduced need for allogeneic blood transfusion.[12,47,48] Thus, 11 randomised trials have been published investigating different algorithms and triggers, different devices, and different subgroups of cardiac surgery patients.[47] Special attention has been given to the study by Weber *et al.*[45] which was terminated prematurely after an interim analysis showed a significantly improved survival using VHA-guided therapy. The study specifically investigated the use of a VHA-guided

algorithm in patients with coagulopathy or severe postoperative bleeding. Meta-analysis of pooled data from 1089 patients suggests a benefit in terms of reduced blood requirements, even if insufficient data were available on mortality.[12] However, most trials have a high risk of bias.[47,48] Finally, in cardiac surgery with CPB, it might be an advantage to combine VHA with platelet function assays.[37,45,46,49]

4.1.5. Postoperative evaluation of coagulation status

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

Currently, it remains uncertain whether low postoperative fibrinogen levels are causally associated with postoperative bleeding.[50] In paediatric cardiac surgery, post-CPB plasma fibrinogen concentration appears to influence blood loss, with a fibrinogen concentration of at least 1.5 g l^{-1} or an MCF of at least 3 mm accurately predicting excessive blood loss.[51] Prediction of postoperative bleeding volume using haemostatic assessment, including VHAs, is not convincing.[52,53] However, haemostatic deficiencies are not the sole cause of postoperative bleeding and attempts to predict bleeding are often thwarted by the presence of more obvious surgical causes. The ability to rapidly exclude haemostatic impairment is of great value as normal haemostasis in a patient with postoperative bleeding would indicate a surgical cause of bleeding and this differentiation might speed up the decision to re-operate. Two RCTs, with a total of 192 patients, investigated the use of VHAs in the treatment of excessive postoperative bleeding or suspected coagulopathy in cardiac surgery patients.[42,45] Both studies suggest a reduced need for allogeneic transfusion and the study by Weber *et al.*[45] showed reduced mortality. Six other RCTs investigating intraoperative use of VHA-monitored haemostatic treatment also applied the interventional algorithm to the beginning of the postoperative period from 2 h postoperatively up until the entire ICU stay.[32,36,37,39,40,46]

4.1.6. Are patient outcomes improved by algorithms that incorporate monitoring for perioperative haemostatic management?

Recommendations

We recommend the application of intervention algorithms incorporating pre-defined triggers and targets based on VHA coagulation monitoring to guide individualised haemostatic intervention in the case of perioperative bleeding. **1C**

If VHA is not available we recommend the application of intervention algorithms incorporating pre-defined triggers based on conventional coagulation tests. **1C**

Long turnaround times may preclude the use of some tests in emergency situations. However, implementation of VHA monitoring appears rational if the alternative is haemostatic management guided by clinical judgement alone. In a recent analysis, the use of VHAs was found to be effective in reducing RBC transfusion, platelet transfusion and FFP transfusion.[12] VHAs were also cost-saving and more effective than SLTs in patients undergoing cardiac surgery and in trauma patients.

Antithrombin III (AT III), a potent anticoagulant with independent anti-inflammatory properties, irreversibly inhibits serine proteases (e.g. activated factor X and thrombin). There have often been arguments to increase the antithrombin concentration to supranormal values because the activity of pro-inflammatory and pro-coagulant molecules are increased in critically ill patients.[54] However, in a recent Cochrane systematic review, the effect of supplementation with AT III in critically ill patients was found to be of questionable value based on the available evidence, and there was an increased risk of bleeding in those receiving AT III to attain supranormal values.[55]

Nevertheless, supplementation with AT III in a cardiac surgical setting to avoid FFP transfusion may be considered as an option, although one has to consider the extensive cost and the risk of heparin rebound in the early postoperative period.[56]

In the paediatric liver transplantation population, the AT III levels are often found to be reduced postoperatively but there is still controversy as regards management of this deficit.[57]

4.2. 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.

Recommendations

We suggest preoperative platelet function testing only in association with a positive bleeding history. **2B**

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

Bleeding time is influenced by many variables and is not useful for stratifying bleeding risk. **C**

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

In thrombocytopaenic patients, several tests such as platelet indices, Multiplate, Cone and Plate(let) Analyser

(CPA, Impact-R), viscoelastic methods and PFA-100 (Platelet function analyser-100) are rapid and easy to perform.[58] However, PFA-100 lacks sensitivity for known platelet secretion defects and, while others appear superior in this regard, the evidence remains sparse in thrombocytopaenic patients. Current evidence indicates that the flow cytometric marker for activation of P-selectin and surface coverage by the Cone and Plate(let) analyser may predict bleeding in selected thrombocytopaenic populations.

4.2.2. Preoperative platelet function testing in different clinical settings

4.2.2.1. Trauma

In the setting of traumatic brain injury with trauma-induced coagulopathy, multi-modality monitoring of platelet function appears to detect patients at risk of bleeding and may, together with TEG/ROTEM, guide transfusion management.[26,59]

4.2.2.2. Cardiac surgery

Preoperative platelet function testing may increase the predictive value of postoperative bleeding in patients undergoing CABG surgery.[60] Platelet dysfunction measured during re-warming and postprotamine has been shown to be independently associated with high blood loss in cardiac surgery.[61]

In a recent large observational study in adult cardiac surgery examining the predictive value of multiple electrode platelet aggregometry (Multiplate), the ADP test (adenosine diphosphate test) and the TRAPtest (thrombin receptor activator peptide test) were found to predict the requirement for perioperative blood transfusion.[62]

A recent systematic review on the role of point-of-care platelet function testing in predicting postoperative bleeding concluded that incorporation of point-of-care platelet function tests into transfusion management algorithms was associated with a reduction in blood loss and transfusion requirements following cardiac surgery.[63] However, this has been disputed by others due to the lack of high-quality studies.[64]

In a recent European guideline on the role of platelet function testing in patients undergoing percutaneous coronary intervention, the authors advocate the use of VerifyNow and Multiplate as point-of-care tests to prevent methodological errors during testing and to allow for easier generalisation of test results.[65] Nevertheless, the authors recommend that platelet function results should only be interpreted in the clinical and angiographic context of each individual as platelet reactivity to ADP should not be the only criterion on which to base the clinical decision.

In an observational study of patients undergoing off-pump CABG surgery the authors sought to compare the role of preoperative platelet function testing by comparing VerifyNow, TEG, AggreGuide, Plateletworks, vasodilator-stimulated phosphoprotein (VASP) phosphorylation and light transmission aggregometry (LTA).[66] However, they observed little correlation among the platelet function tests and little correlation between those assays and perioperative bleeding.

4.2.2.3. Neurointerventional procedures

Despite the increasing use of point-of-care platelet function assays, in a recent guideline, the authors state that most of the current evidence is extrapolated from other settings and there is insufficient data to recommend routine platelet function testing prior to neuroinvasive procedures.[67]

4.2.3. Genetic testing of patients with suspected platelet function disorders

Inherited platelet function disorders (PFDs) may be associated with normal or reduced platelet counts. PFDs account for a significant proportion of bleeding diatheses and the identification of the underlying genetic defects remains challenging.[68,69] The majority of patients with PFDs have normal platelet counts and mild bleeding symptoms but are at increased risk of bleeding in the context of trauma, surgery or childbirth.[70] In these patients, a significant number of mutations are heterozygous and, in isolation, are unlikely to cause extensive bleeding. The genetic complexity of PFDs highlights plausible candidate genes for targeted analysis.[71]

5. Anaemia management

5.1. Preoperative correction of anaemia

5.1.1. Introduction

Perioperative anaemia increases the risk of numerous complications, such as acute kidney injury.[72] Preoperative anaemia has been shown to be predictive for perioperative transfusion of allogeneic blood products such as RBCs, which itself carries a significant risk of adverse events and mortality.[73] A large study estimated the prevalence of preoperative anaemia to be 31.1% in women and 26.5% in men.[74] High rates have been reported in some orthopaedic procedures such as total knee arthroplasty (TKA), whereas lower rates have been observed in other orthopaedic procedures such as treatment of hip fracture.[75]

5.1.2. Preoperative assessment of anaemia

Recommendation

Preoperative anaemia in adults and children appears to be a strong predictor for perioperative blood transfusion across various types of conditions and surgeries and may be associated with adverse events. **B**

We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. **1C**

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

Anaemia is associated with prolonged bleeding times, probably caused by the rheological effect of RBCs on the margination of platelets inside the vessel, which ultimately influences platelet interaction with the endothelium and thus primary haemostasis. The degree of anaemia and the impact of low Hct on VHA values remain somewhat unclear, but this may ultimately illustrate the inability of VHA devices to reflect the haemostatic impact of the vascular endothelium.[76,77]

In a recently published retrospective study of 1928 paediatric trauma patients, the initial Hct values were found to correlate significantly with conventional signs of shock and were a strong independent predictor for blood transfusion with a better predictability for the latter than other clinical factors.[78] In an observational retrospective study, the RBC volume was found to be a predictor for perioperative blood cell transfusion in orthopaedic major joint replacement.[79] Similarly, among 843 women undergoing major gynaecological surgery, retrospective analysis showed that preoperative anaemia was a common finding and was associated with increased RBC transfusion.[80] In cardiac surgery, retrospective data from 943 patients demonstrated a high prevalence of preoperative anaemia which significantly correlated with higher transfusion rates.[81]

The implementation of a patient blood management (PBM) programme, which included patient assessment 4 weeks before surgery, was shown to be effective in reducing the rate of preoperative anaemia and lowering the rate of transfusion as compared to before implementation of the programme.[82] Other groups have successfully used PBM programmes with testing at about 3 weeks preoperatively.[83–85]

Assessment of patients 3 to 8 weeks before elective surgery provides enough time to initiate treatment and for this to take effect. This recommendation is also in agreement with current consensus[86] and practical recommendations.[87]

Accurate diagnosis of anaemia requires investigation after it has been determined that haemoglobin levels are low.[86]

5.1.3. Preoperative treatment

Recommendation

We recommend treating iron deficiency with iron supplementation. **1B**

We recommend the use of intravenous iron in preference to oral iron. **1C**

Most (though not all) studies report that preoperative oral iron supplementation is effective in raising haemoglobin concentration and decreasing perioperative transfusion. Two recent publications, a consensus statement[86] and practical recommendations,[87] both advocate correction of iron levels before orthopaedic surgery.

Oral iron supplementation may be suitable for a high proportion of patients, and any side-effects are usually mild.[88]

In a prospective study, female patients with gynaecological ailments and anaemia were treated preoperatively with iron sucrose and haemoglobin concentration increased by a mean average of 5.15 g dl^{-1} ($P < 0.001$) within 30 days of treatment.[89]

Also, in another prospective study of 20 patients with colorectal cancer, a single dose of intravenous ferric carboxymaltose given preoperatively increased haemoglobin levels by 1.8 g dl^{-1} ($P < 0.001$).[90]

A systematic review concluded that patients with preoperative iron deficiency anaemia may have an earlier and more robust recovery of haemoglobin concentration with preoperative intravenous iron than with oral iron supplementation.[91]

Recommendation

If other causes of anaemia have been excluded or treated, we suggest erythropoietin-stimulating agents. **2B**

A meta-analysis evaluated the effectiveness of erythropoietin-stimulating agents in patients undergoing knee or hip arthroplasty. Preoperative use of erythropoietin-stimulating agents reduced autologous blood transfusion, relative risk 0.48 ($P < 0.0001$), and mean haemoglobin levels were 0.71 g dl^{-1} higher than for control groups ($P < 0.00001$).[92] A systematic review also concluded that a short preoperative regimen of erythropoietin may significantly reduce transfusion rates.[91]

The effect of erythropoietin on transfusion rates has been shown to be significant in two separate studies of hip replacement patients with preoperative haemoglobin levels of 10.0 to 13.0 g dl^{-1}.[93,94]

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.[86]

In a simulation of 50 000 individual patients, based on data from controlled trials, preoperative administration of erythropoietin was predicted to be more cost-effective than either autologous blood donation or an allogeneic blood transfusion strategy.[95]

Recommendation

If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. **2C**

5.1.3.1. Other possible treatment approaches

Recommendations

In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. **1C**

In non-cancer patients with preoperative anaemia scheduled for elective major surgery, we recommend postponing surgery until anaemia has been corrected. **1C**

In a prospective study, patients undergoing hip or knee arthroplasty were treated, according to a blood conservation algorithm, with oral or intravenous iron and erythropoietin if they had preoperative haemoglobin concentration less than 12 g dl^{-1} (women) or 13 g dl^{-1} (men).[96] Compared with a retrospective comparison group, significantly fewer patients received blood transfusions for both hip and knee procedures ($P < 0.001$ and $P = 0.001$, respectively). The length of stay in hospital and rate of readmission also decreased significantly for both procedures.

Results from a retrospective study described total hip arthroplasty in Jehovah's Witnesses following a perioperative blood management strategy.[84] Patients with preoperative haemoglobin (Hb) less than 12.0 g dl^{-1} were treated with erythropoietin for 3 weeks before surgery, plus oral iron and folate. None of the 53 patients received blood transfusion and there were no mortalities. Also, a retrospective study of patients undergoing cardiac valve replacement showed that erythropoietin and intravenous iron, given for 4 weeks preoperatively, significantly decreased the rate of RBC transfusion ($P = 0.01$) and was associated with decreased perioperative morbidity and in-hospital mortality.[97] A recent consensus statement also advocated the preoperative use of erythropoietin plus iron in patients who are anaemic, likely to refuse blood products (e.g. Jehovah's Witnesses), or who are considered likely to have postoperative anaemia.[98]

Leahy *et al.*[99] described the introduction of a perioperative PBM programme to a tertiary hospital. The PBM programme included optimising erythropoiesis, minimising blood loss and bleeding and optimising the reversal of anaemia with intravenous iron. The mean number of RBC units transfused per patient decreased by 26% compared with before the PBM programme was introduced. In another study of patients undergoing knee, hip, or spinal surgery a PBM programme consisting of the management and treatment of preoperative anaemia, the reduction of intraoperative blood loss by surgical, anaesthesiological and pharmacological techniques, and a lowering of the transfusion threshold to a Hb 8.0 g dl^{-1} or less was investigated retrospectively.[82] Anaemic patients were treated daily for 4 weeks before surgery with intravenous iron carboxymaltose, erythropoietin, vitamin B12 and folic acid. As compared with before implementation of the program, the rate of transfusion decreased significantly for all three types of surgery and the incidence of anaemia immediately before surgery decreased significantly for patients undergoing hip and knee surgery. Also of note, improved surgical technique played a significant role in reducing the intraoperative blood loss.[82]

5.1.4. Postoperative anaemia

Recommendation

In patients who are anaemic following surgery, we suggest the use of intravenous iron. **2C**

Evidence from two randomised, controlled studies in patients undergoing TKA[75] or total hip arthroplasty[100] showed that, compared with placebo, iron supplementation significantly reduced the rate of transfusion. Both studies showed that the reduction in transfusion was more pronounced in anaemic patients compared with non-anaemic patients.[75,100] In addition, administration of intravenous iron sucrose and ferric carboxymaltose preparations of iron were found to be cost-neutral.[100]

In contrast to these results, multiple randomised, placebo-controlled studies have shown that iron supplementation for anaemia after surgery had no effect on transfusion requirements in the settings of cardiac surgery,[101–104] orthopaedic surgery,[103,105–108] or surgery in colorectal cancer patients.[109]

It is possible that surgery induces changes in iron metabolism, which could explain why postoperative iron supplementation is ineffective.[110]

There is limited evidence to suggest that intravenous iron may be advantageous in treating postoperative anaemia. In a randomised, controlled study, intravenous iron achieved normal haemoglobin levels significantly more frequently than in patients receiving oral iron.[75] In another randomised, controlled study, serum ferritin levels were higher at hospital discharge in patients who had taken intravenous iron compared with those who had received oral iron.[102]

6. Optimising circulation

6.1. 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 reserve, priority goes to intravascular volume replacement with plasma substitutes devoid of 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. 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 adequately powered controlled studies, the limited representation of clinical scenarios and the absence of a consistent terminology. Several meta-analyses have assessed studies that evaluated the impact of perioperative fluid therapy on patient outcomes[111–115]; however, few of these studies qualify to serve as a basis for recommendations. Better and more recent studies have been performed in abdominal surgery,[116,117] where perioperative fluid needs may differ considerably from other surgical procedures. Patients at high risk are often excluded, even if they represent the typical collective.[113] The impact of perioperative fluid management on outcome cannot be isolated from other interventions[118] and only a few prospective trials included details of therapeutic strategy beyond fluid therapy. Perioperative fluid management must be embedded in a larger perioperative therapeutic concept to impact on patient outcome.

6.3. Optimising macrocirculation

6.3.1. Pre-load optimisation

Recommendations

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

In cases of uncontrolled bleeding, we suggest lower thresholds for cardiac pre-load and/or permissive hypotension. **2C**

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. The most recent meta-analyses[111,112,114,115] concluded that a goal-directed approach, where therapy aims to maintain tissue perfusion by flow-based haemodynamic monitoring and therapeutic interventions, reduces mortality, postoperative organ failure and surgical complications, especially in high-risk surgical patients.[113]

Recommendation

We recommend the avoidance of hypervolaemia secondary to crystalloids or colloids to a level exceeding the interstitial space in the steady state, and beyond an optimal cardiac pre-load. **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).[119] Artificial hypervolaemia predisposes patients to interstitial oedema, which appears to be associated with perioperative mortality.[120]

Recommendation

We recommend against the use of CVP and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimisation of pre-load during severe bleeding. Dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead. **1B**

CVP remains the most widely used clinical marker of volume status, despite numerous studies showing no association between CVP and circulating blood volume.[121] Several studies have demonstrated that dynamic parameters such as SVV or PPV provide better prediction of fluid responsiveness in mechanically ventilated patients with a normal heart rhythm, even when a 'grey zone' to determine the ideal threshold of these dynamic parameters is taken into account.[122] To use these dynamic parameters correctly there are some prerequisites.[123] Fluid challenges and the leg-raising test represent simple and valid alternatives.[124]

The most extensively studied and successfully used method to maximise cardiac pre-load is the oesophageal Doppler device. No data prove the superiority of substitution regimens guided by specific devices or specific algorithms.

6.4. Considerations for microcirculation

6.4.1. Crystalloids versus colloids

Recommendations

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**

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

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

6.4.2. Transfusion target

Recommendations

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

Continuous haemoglobin monitoring can be used as a trend monitor. **C**

During bleeding, patients may be less able to tolerate anaemia because compensatory mechanisms may be impaired. However, it is not known whether the lowest tolerable haemoglobin concentration is determined by volume status. Data from patients undergoing surgery or in intensive care indicate that a restrictive transfusion regimen (Hb concentration maintained at 7 to 8 g dl^{-1}) is as effective and well tolerated as a liberal transfusion

regimen (Hb concentration maintained at 9 to 11 g dl^{-1}).[125,126] One RCT in surgical oncology patients favoured a more liberal transfusion trigger.[127] Considering the lack of benefits from higher haemoglobin concentrations, and the potential side-effects of transfusing allogeneic blood,[128] blood transfusions to raise haemoglobin concentrations above 9 g dl^{-1} cannot be supported.

6.4.3. Oxygen fraction

Recommendation

We recommend that the inspiratory oxygen fraction should be high enough to prevent arterial hypoxaemia in bleeding patients, while avoiding excessive 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 could endanger oxygen delivery. However, it has been demonstrated that the side-effects of HV (e.g. vasoconstriction) may worsen patient outcomes during acute myocardial infarction[129] or surgery.[130] Overall, current evidence supports the use of HV to achieve physiological arterial oxygen partial pressures during haemorrhagic shock.

6.4.4. Monitoring tissue perfusion

Recommendation

We recommend repeated measurements of a combination of Hct/haemoglobin, serum lactate and base deficit 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. SVV, PPV), CO_2 gap and central venous oxygen saturation. **1C**

6.4.5. Normovolaemic haemodilution

Recommendations

We suggest the use of ANH in selected settings. **2C**

We recommend against ANH in combination with controlled hypotension. **1B**

In patients with pre-existing or acquired coagulopathy we suggest that the use of ANH is considered carefully. **2C**

7. Transfusion of labile blood products

7.1. Infectious risk of allogeneic blood components

Recommendations

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

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

Although transfusion of labile blood products may save lives, it can also do harm, resulting in poorer patient outcomes. At the end of the 1980s, the emergence of HIV, and the discovery that it could be transmitted by the transfusion of labile blood components, put into question the safety of blood. Pioneer work started in France with the development of blood transfusion committee monitoring systems, resulting in a national haemovigilance network in 1994,[131] followed by similar programmes in other European countries, Canada, and recently the United States.[132] On a European level, haemovigilance began with the Resolution of the European Council, published in 1995, with the aim of improving public confidence in the safety of blood products. European Blood Directives that give mandatory rules for collection, testing, processing, storage, and distribution of human blood and blood components and which include Directives dealing with haemovigilance were published between 2003 and 2005.[133,134] The word haemovigilance is derived from the Greek 'haema' (blood) and the Latin 'vigilans' (watchful). According to de Vries *et al.*[135] haemovigilance is defined as 'a set of surveillance procedures covering the whole transfusion chain from the collection of blood components to the follow-up of its recipients, intended to collect and assess information on unexpected or untoward effects resulting from the therapeutic use of labile blood products and to prevent their occurrence and their recurrence'.

Several reports have been published by different national haemovigilance systems.[136–139] From these different reports it can be concluded:

(1) Blood transfusion is relatively well tolerated when compared with medicinal drugs
(2) The majority of preventable adverse reactions are due to clerical errors
(3) Some adverse reactions have to be considered as an inherent risk of blood transfusion as they are often not avoidable (e.g. anaphylactic reactions)
(4) Although current haemovigilance systems show significant conceptual and organisational differences, they may report similar outcomes
(5) Haemovigilance systems may be used to improve not only the safety of blood transfusion, but also appropriate use
(6) Successful haemovigilance systems not only indicated how safety should be improved but also reported on the relative efficacy of various measures
(7) Haemovigilance systems could be used to assess the safety of alternatives for allogeneic blood transfusion such as the use of cell savers.

Recommendation

We recommend pathogen inactivation for FFP and platelets. **1C**

Although contamination of blood components with infectious agents represents a continuing challenge in transfusion medicine, rates of infection with known blood-transmitted pathogens (e.g. HIV, HBV, HCV) are low following the implementation of high sensitivity testing methods. However, (re-) emerging pathogens remain a concern. Potential donors are asked questions on travel history, drug abuse, sexual behaviour, and others; however, residual risks remain.[140] 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. The introduction of molecular biology with the nucleic acid amplification testing (NAT) assays has reduced the classical 'window period' to what is now called the 'eclipse phase' in which detectable concentrations of viral nucleic acid are present in plasma.[141] These NAT assays are generally applied to classical transfusion-transmitted viruses HIV, HBV and HCV.[142–144]

Blood monitoring systems must develop procedures allowing the identification and recognition of a transfusion-transmission threat, the quantification of the risk, and finally, the reduction of the associated risk to transfusion recipients.[145]

Despite improvements in laboratory diagnostics, donor selection and blood collection techniques, the risk of bacterial and insect-borne contamination, mainly in platelet units (but also in RBC units), and the risk of transmission of untested and emerging transfusion-transmitted viruses remain. Application of pathogen inactivation techniques addresses this problem. Current methods either target nucleic acids or cell membranes.[146] They are active on bacteria, protozoa, contaminating leukocytes, known viruses and unknown transfusion-transmissible agents, but not on prions. They include solvent/detergent (SD), methylene blue, amotosalen and riboflavin technologies: apart from the SD method, all require the use of visible or ultraviolet light. Although these methods slightly reduce the concentration of coagulant proteins in the plasma, the concentrations remain within accepted ranges.[147]

Platelet components are treated either with the amotosalen or the riboflavin methods. The therapeutic efficacy and safety of pathogen-reduced platelets appear to be similar to conventional platelets.[146,148] However, in most trials, transfusion of pathogen-reduced platelets resulted in lower platelet count increments, a shorter interval between platelet transfusions and an increased number of platelet transfusions per patients.[146]

Pathogen inactivation of RBC products appears more challenging.[149] Two methods are currently in commercial development: the whole blood photochemical inactivation using riboflavin and ultraviolet light (Mirasol System) and the RBC chemical inactivation using S-303 and glutathione (GSH: Intercept system).[150]

Recommendation

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

Leukodepletion refers to the process of removing white blood cells from a unit of RBCs or platelets to a standardised degree. This is accomplished through either removal of the buffy coat following centrifugation or pre-storage filtration. The current consensus is that leukodepletion has defined indications in the prevention of three complications of blood transfusion: febrile non-haemolytic transfusion reactions (HTRs), platelet refractoriness due to alloimmunisation to human leukocyte antigen and transmission of cytomegalovirus.[151] In these indications, leukodepletion has been shown to be clinically effective and cost-effective.[151]

Most European countries adopted universal leukodepletion in the late 1990s on the suggestion that leukodepletion might reduce the transmission of Creutzfeldt–Jacob disease and on the basis of accumulating evidence of leukocyte-mediated transfusion-related immunomodulation. Although leukocyte depletion shows a reduction in blood prion infectivity of between 58 and 72%,[152] it does not constitute a definite solution for removal of prions from blood components. The development of complementary methods, such as prion removal filters, would further minimise the blood-borne risk of Creutzfeldt–Jacob disease transmission.[153] However, discordant results of several meta-analyses suggest that if universal leukodepletion does diminish transfusion-related immunomodulation, then the clinical effects are difficult to capture in clinical studies. Since 1998, only one double-blind RCT reported reduced infection rates and in-hospital mortality rates after cardiac surgery in patients randomised to pre-storage leukodepleted blood compared with buffy-coat depleted blood.[154] As a result of the limited evidence, the rationale for applying universal leukodepletion remains highly debated by the scientific community.[155,156] Unfortunately, this debate is not likely to be resolved, as universal leukodepletion has become the standard of care in most Western countries.

7.2. Immunological and non-immunological complications associated with the transfusion of labile blood components

Recommendations

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

We recommend a male-only donor policy for plasma-containing blood products to prevent the onset of TRALI. **1C**

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

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

One of the most effective ways to reduce transfusion-related complications is to introduce a restrictive transfusion protocol, that is transfuse only what is really necessary (RBCs, plasma or platelets) and only when it is really necessary. Two recent meta-analyses assessed the effects of transfusion thresholds (based on a specified haemoglobin or Hct value) on the use of RBC transfusions and on clinical outcomes.[157,158] These meta-analyses included 19 trials ($n = 6264$ patients)[157] and 31 trials ($n = 9813$ patients),[158] respectively, and they demonstrated that restrictive transfusion strategies are well tolerated in most clinical settings and are associated with a reduction in the number of patients being transfused and in the number of RBC units transfused. In patients with UGIB, a restrictive transfusion strategy (Hb concentration maintained at 7 g dl^{-1}) was associated with improved outcomes compared with a liberal one (Hb concentration maintained at 9 g dl^{-1}).[126] In patients with septic shock, a restrictive transfusion strategy did not alter outcomes, although it significantly reduced patients' exposure to allogeneic RBC transfusion.[159] However, the best transfusion strategy still remains to be determined in some particular populations, for instance patients undergoing cardiovascular surgery.[160] After cardiac surgery, a restrictive transfusion strategy was not found to be superior to a liberal one with respect to postoperative morbidity, and might even be associated with an increased 90-day mortality.[161] Also, in patients with acute coronary disease, the question remains unanswered, as there are no prospective randomised trials, and the same is true for patients with traumatic brain injury. In a small study of surgical oncology patients, de Almeida *et al.*[127] reported that, compared with a restrictive transfusion strategy (Hb concentration maintained at 7 g dl^{-1}), a more liberal RBC transfusion strategy (Hb concentration maintained at 9 g dl^{-1}) could be associated with fewer major postoperative complications.

Although blood transfusion in most Western countries is very well tolerated, patients continue to be put at risk by human errors at all stages of the transfusion process. The 2014 annual SHOT report analysed 3017 reports.[162] The majority of incidents were caused by human error and these accounted for 77.8% of reports: a steady increase from 2011, and an ongoing major concern for transfusion safety. In addition to instances of failures in patient identification, communication and documentation, several reports indicated poor clinical decision-making, or confusion as a result of too many clinical opinions with poor handover.[162] In 2014, the estimated risk of death associated with the transfusion of a labile blood component was calculated at 5.6 per million components issued and the estimated risk of major morbidity was 63.5 per million components issued. Most of these cases were acute transfusion reactions, which included anaphylaxis/hypersensitivity and febrile non-haemolytic reactions. Acute transfusion reactions are now the leading cause of major morbidity associated with transfusion of labile blood components.[162] RBCs are usually associated with febrile-type reactions, plasma (methylene-blue and SD-treated FFP) with allergic reactions, and platelets with both.[162]

HTRs are typically caused by transfusion of RBCs carrying antigens to which the recipient has significant alloantibodies. The most frequent cause of intravascular HTRs is ABO incompatibility attributable to procedural errors. In the 2014 SHOT report, there were 10 ABO-incompatible RBC transfusions, all due to clinical errors.[162]

The objective of haemovigilance systems is to improve patient safety: it is therefore important that hospitals complete their reporting process with an appropriate incident investigation in order that lessons may be learned and practice improved.[163] It should be noted that two thirds of ABO-incompatible red cells transfusion do not result in harm. They will be included in future SHOT reports as 'never events'.[162]

Despite the very useful information gained about transfusion reactions, the main risks remain human factors. Correct patient identification and adherence to basic procedures remains the key to safer practice.[138]

TRALI is potentially life-threatening and occurs within 6 h of transfusion of plasma-containing blood products.[164] The 2014 SHOT report includes nine cases of suspected TRALI (from a total of 1681 reviewed cases) resulting in two possible/probable related deaths, and seven major morbidities.[162] In one of these cases, cryoprecipitate was implicated: the patient received a pool in which three female donors had concordant class 1 and class 2 antibodies.

Plasma from female donors has been particularly implicated in the pathogenesis of antibody-mediated TRALI. Therefore, most blood collection organisations have implemented the preferential use of plasma from male donors as a precautionary measure to reduce TRALI. A recent meta-analysis including 10 studies which implemented a 95 to 100% male-only plasma donation policy reported a significant reduction for the risk of TRALI after the introduction of this strategy.[165] Although none of these studies were randomised trials and only two of them were prospective, the risk of bias of patient selection was low. Heterogeneity was high for all studies combined, and low for pre-defined subgroup analysis.

Transfusion-associated graft-versus-host disease (TA-GVHD) is a generally fatal immunological complication of transfusion, involving the engraftment and clonal expansion of viable donor lymphocytes contained in labile blood components in both immunocompetent and compromised hosts.[166] Typical features of TA-GVHD include fever, maculopapular skin rash affecting the palms, diarrhoea, liver dysfunction, pancytopaenia and bone marrow hypoplasia occurring less than 30 days following transfusion. A total of 14 cases of TA-GVHD have been reported to SHOT since 1996: all were fatal.[167]

Transfusion-associated circulatory overload (TACO) is increasingly being recognised as an important cause of mortality and morbidity by European haemovigilance systems. The 2014 SHOT report analysed 91 cases compared with 96 in 2013.[162] The age of patients ranged from 1 to 98 years. Most of the cases occurred on the wards and followed routine transfusion. However, the incidence of perioperative TACO appears similar to previous estimates in non-surgical populations.[168] In the 2014 SHOT report, TACO was associated with six out of the 13 deaths recorded and with 36 cases of major morbidity. It should be noted that the true extent of TACO remains unclear, as a formal definition of it appears hard to achieve. The current International Society of Blood Transfusion (ISBT) definition of TACO (revision in progress) includes the combination of any four of the following five items within 6 h of transfusion: acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary oedema, and evidence of positive fluid balance. As for other complications associated with blood transfusion, human errors are common, which support the role of haemovigilance systems and of adequate education in transfusion medicine.[169]

The key to reducing TACO is to prevent its occurrence, which begins with the identification of at-risk patients.[168–172] Identified risk factors include being at an extreme of age, female sex, having a positive fluid balance in the 24 h preceding the transfusion, pre-transfusion left ventricular dysfunction leading to congestive heart failure, renal dysfunction and the rate of transfusion. Interestingly, transfusion volume did not appear to be a risk factor, although the proportion of events associated with death or severe morbidity tended to increase with the number of transfused units. In Europe, the incidence of TACO was higher with RBCs than FFP and lowest with platelet concentrates.[169,171] In the US, FFP is considered the higher-risk transfusion product.[170] This difference might be because in the US, FFP is used to neutralise VKAs as PCCs are not available.[171]

Once high-risk individuals have been identified, prevention of TACO will require the widespread use of pre-transfusion checklists and the implementation of non-emergency transfusion protocols[170,171] including a slow infusion rate. The use of pre-transfusion diuretics has been also suggested. Most authors recommend careful monitoring and supervision of the transfusion process in high-risk individuals.[169–171]

7.3. Storage lesions

Recommendation

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

The potential link between prolonged duration of storage of RBCs and adverse clinical outcomes has been highly debated in the literature. Several meta-analyses have resulted in conflicting results.[173–175] However, three recent large multi-centre prospective studies did not demonstrate any significant effect of red cell storage duration on major morbidity and mortality in high-risk patients. In the first double-blind controlled trial (ARIPI trial: $n = 377$) premature infants with birth weight less than 1250 g were randomised to receive transfusions of RBCs stored for 7 days or less (mean age, 5.1 ± 2.0 days) or standard-issue RBCs in accordance with standard blood bank practices (mean age, 14.6 ± 8.3 days).[176] There was no difference between the two groups regarding the primary outcome, which was a composite measure of major neonatal morbidities. In the second blinded trial, critically ill adult patients (ABLE trial: $n = 2430$) were randomised to receive either RBCs stored for less than 8 days (mean age, 6.1 ± 4.9 days) or standard-issue RBCs (mean age, 22.0 ± 8.4 days).[177] There was no difference between the two groups regarding the primary outcome (90-day mortality), or in any of the secondary outcomes (major morbidity and hospital length of stay). In the third trial, patients at least 12 years of age, who were undergoing complex cardiac surgery (RECESS trial, $n = 1098$), were randomised to receive either RBCs stored for 10 days or less (mean age, 7.8 ± 4.8 days) or for 21 days or more (mean age, 28.3 ± 6.7 days) for all intraoperative or postoperative transfusions.[178] There was no difference between the two groups regarding the primary outcome (a change in the Multiple Organ Dysfunction Score), or 7-day and 28-day mortality. Although these studies did not address the issue of whether the use of RBCs stored for very prolonged periods (up to 42 days) results in harm, they did not observe any clinically important improvements in outcomes with fresh RBC transfusions.

7.4. Cell salvage

Recommendations

We recommend the use of red cell salvage, which is helpful for blood conservation in major cardiac and orthopaedic surgery. **1B**

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

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

We suggest that cell salvage is not contraindicated in cancer surgery, provided that blood aspiration close to the tumour site is avoided and leukodepletion filters are used. **2C**

Intraoperative and postoperative cell salvage reduces the need for allogeneic RBC transfusion in major orthopaedic surgery, such as hip and knee replacement.[179–181] Other indications for intraoperative cell salvage (ICS) may include spinal surgery, hepatic transplant and abdominal aortic aneurysm repair.[182,183] However, evidence for the use of cell salvage in individuals undergoing abdominal or thoracic trauma surgery remains equivocal.[184]

In cancer surgery, there is concern about the risk of re-infusing malignant cells, which could cause metastases. Certainly, aspiration of blood from close to the tumour site should be avoided. Leukodepletion filters appear to be an effective method for removal of malignant cells from ICS blood.[185] More recent non-randomised studies in urological cancer surgery and metastatic spinal surgery have shown ICS to decrease the need for allogeneic RBC transfusion with no apparent risk of decreased long-term survival from an oncological perspective.[186–188]

Contamination of the surgical field (e.g. bowel surgery, penetrating abdominal trauma or infected wounds) has typically been considered as a contraindication for ICS. However, after laparotomy for abdominal trauma, the literature shows no difference in infection rates in patients receiving allogeneic blood components or cell-salvaged blood. An RCT in patients undergoing laparotomy for abdominal injuries demonstrated that ICS significantly reduced allogeneic blood usage, without increasing postoperative infection or fatality rates.[189]

During the peripartum period, shed blood can be contaminated with amniotic fluid and foetal blood, so reinfusion carries a theoretical risk of amniotic fluid embolus and alloimmunisation of the mother.[190] However, amniotic fluid embolism is no longer regarded as an embolic disease but rather as a rare anaphylactoid reaction to foetal antigens. The contamination of the salvaged blood by foetal Rh-mismatched RBCs can be dealt with using Rh immunoglobulins, and ABO incompatibility tends to be a minor problem as ABO antigens are not fully developed at birth. Although the role of cell salvage as a blood-saving measure in obstetrics is becoming more common, the published evidence of its quality and safety remains weak (800 documented procedures and about 400 patients transfused with salvaged blood).[190,191] Therefore, ICS in obstetrics should be considered in patients at high risk of haemorrhage or in cases where allogeneic blood transfusion is difficult or impossible.

7.5. Plasma and platelet transfusion

Recommendations

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

We recommend early and targeted treatment of coagulation factor deficiencies in the plasma. Sources of coagulation factors are coagulation factor concentrates, cryoprecipitate or high volumes of plasma, depending on the clinical situation, type of bleeding, type of deficiency and resources provided. **1B**

In the treatment of acquired coagulation factor deficiency, we suggest the consideration of a ratio-driven protocol (RBC:plasma:platelet concentrates) early in uncontrolled massive bleeding outside the trauma setting followed by a goal-directed approach as soon as possible. **2C**

We suggest coagulation factor concentrates for the primary treatment of acquired coagulation factor deficiency due to their high efficacy and their minimal infectiousness. **2C**

We recommend against indiscriminate use of plasma transfusion in perioperative bleeding management. **1C**

We suggest platelet concentrate transfusion in bleeding situations clearly related to antiplatelet drugs or thrombocytopaenia less than $50 \times 10^9\ l^{-1}$. **2C**

A small RCT of pre-procedural FFP and/or platelet support ($n = 60$) in patients with cirrhosis demonstrated that a transfusion strategy based on TEG parameters resulted in a substantial reduction in transfusion and no increase in bleeding complications.[192]

8. General coagulation management

8.1. Indications, contraindications, complications and doses

Recommendations

Fibrinogen concentration of less than 1.5 to 2 g l^{-1} *is considered as hypofibrinogenaemia in acquired coagulopathy and is associated with increased bleeding risk.* **C**

We recommend treatment of hypofibrinogenaemia in bleeding patients. **1C**

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

In cases where fibrinogen concentrate is not available we suggest cryoprecipitate at an initial dose of 4 to 6 ml kg^{-1}. **2C**

Plasma transfusion alone is not sufficient to correct hypofibrinogenaemia. **C**

In cases of bleeding and low factor XIII activity (e.g. <30%) we suggest administration of factor XIII concentrate (30 IU kg^{-1}*).* **2C**

In severe perioperative bleeding we recommend that patients on VKAs should be given PCC and intravenous vitamin K before any other coagulation management steps. **1B**

Prolonged INR/PT or VHA clotting times alone are not an indication for PCC in bleeding patients not on oral anticoagulant therapy. **C**

We recommend against the prophylactic use of rFVIIa due to increased risk of fatal thrombosis. **1B**

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

We recommend tranexamic acid to prevent bleeding during major surgery and/or treat bleeding due to (or at least suspected) hyperfibrinolysis (e.g. a dose of 20 to 25 mg kg^{-1}). **1B**

We suggest the use of DDAVP under specific conditions (acquired VWS). **2C**

Based on the current literature, there is no evidence to recommend antithrombin supplementation in elective surgical patients while they are bleeding.

We recommend structured staff education and training. **1C**

8.2. Correction of confounding factors

Recommendations

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

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

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

We recommend that calcium should be administered during massive transfusion if calcium concentration is low, to preserve normocalcaemia (>0.9 mmol l^{-1}). **1B**

We suggest that endovascular embolisation is a well tolerated alternative to open surgical intervention after failed endoscopic treatment for non-variceal UGIB. **2C**

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

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

8.3. Cost implications

Recommendations

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

Tranexamic acid can reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several major surgical and trauma settings. **B**

We recommend restricting the use of rFVIIa to its licensed indications 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 in selected patients. **A**

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

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

9. Algorithms in specific clinical fields

9.1. Cardiovascular surgery

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

Recommendations

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

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

We recommend prophylactic administration of tranexamic acid before CPB in patients undergoing CABG surgery. **1A**

9.1.1.1. Antiplatelet therapies

9.1.1.1.1. Aspirin

There may be some benefit to aspirin administration up until the day of surgery. A recent, small RCT ($n = 20$) found that continuing aspirin treatment until the day of surgery reduced oxidative and inflammatory responses, as measured from radial artery and coronary sinus blood samples, and myocardial biopsies.[193] The authors also highlighted a potentially beneficial effect on cardiac tissue injury resulting from surgery. Recent research has also suggested that aspirin therapy may be well tolerated up to the time of surgery. A series of 709 consecutive CABG patients who used aspirin until the time of surgery was compared with 709 matched controls who discontinued aspirin therapy more than 5 days before surgery.[194] The authors found no significant difference between the two groups in intraoperative and postoperative blood loss. Furthermore, there were no significant differences between the groups in terms of postoperative major cardiac event-free survival estimates and cardiac readmissions at 4-year follow-up. The angina-free survival rate was significantly higher in the group who had taken aspirin up to the time of surgery.

9.1.1.1.2. Clopidogrel

A recent meta-analysis of 20 observational studies (23 668 patients) concluded that clopidogrel exposure within 7

days increases the risk of RBC transfusion and bleeding-triggered re-operations, without any benefit on myocardial infarctions postoperatively.[195] The overall mortality rate in those who took clopidogrel up to the time of surgery was also higher. The findings of RCTs have been reflected in a recent retrospective analysis of CABG patients ($n = 715$): a significant association was observed between bleeding and clopidogrel exposure within 5 days before surgery.[196]

A recent meta-analysis of 12 studies reported that continuing antiplatelet therapy (aspirin, clopidogrel) until the time of cardiac surgery was associated with increased blood loss, but carried a low risk of surgical re-exploration for bleeding.[197] The authors concluded that in patients at a high risk of stent thrombosis, this may be acceptable. One retrospective, multi-centre, observational study ($n = 666$) reported that discontinuation of antiplatelet therapies significantly increased major adverse cardiac events (MACEs), myocardial infarction and death, and did not significantly reduce bleeding.[198] However, this study reported cases of both cardiac and non-cardiac surgery, which may be associated with a smaller risk of blood loss.

9.1.1.2. Antifibrinolytic therapy (aprotinin, tranexamic acid and ε-aminocaproic acid)

A meta-analysis of 106 RCTs and 11 observational studies (totalling 43 270 patients) was performed to assess the safety of aprotinin in comparison with other antifibrinolytic treatments.[199] The analysis was largely inconclusive, although the authors did observe that there were, on average, higher mortality and renal failure or dysfunction rates in patients who had been given aprotinin compared with other drugs or no treatment. The authors concluded that concerns about the safety of aprotinin in cardiovascular surgery still remain, and clinicians should be aware of the benefits and risks of the drug.

A meta-analysis of 33 501 patients suggested that mortality may be increased by aprotinin in low-risk to medium-risk cases but not in high-risk cases compared with tranexamic acid and ε-aminocaproic acid (EACA).[200]

9.1.1.3. Coagulation factor replacement therapy

9.1.1.3.1. Antithrombin concentrate

An RCT of 200 patients showed that preoperative infusion of antithrombin to levels of 120% reduced heparin resistance with no adverse effects and prevented a postoperative reduction of antithrombin activity.[201]

9.1.1.3.2. Fibrinogen concentrate

A recent systematic review of four studies ($n = 2154$) found that preoperative fibrinogen levels are poor predictors of postoperative bleeding and could lead to inappropriate treatment in over 80% of treated patients.[202] The authors suggested a plasma fibrinogen cut-off value of 2.5 g l^{-1}, which could reduce the rate of inappropriate interventions. Another recent meta-analysis of 20 studies reiterated that only a weak-to-moderate correlation between fibrinogen and postoperative bleeding existed, and suggested further RCTs are necessary before making recommendations on treatment.[11]

9.1.2. Which therapies can be used to control bleeding intraoperatively?

Recommendations

We suggest tranexamic acid can be applied topically to the chest cavity to reduce postoperative blood loss following cardiac surgery. **2C**

In complex cardiovascular surgery, we recommend fibrinogen concentrate infusion guided by VHA monitoring to reduce perioperative blood loss. **1B**

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

9.1.2.1. Heparin

A recent RCT in elective cardiac valve surgery patients ($n = 38$) compared heparin and protamine dosage based on either heparin monitoring using a point-of-care haemostasis management system, or the standard ACT-based approach.[203] The study found that dosing heparin and protamine based on the haemostasis management system decreased the incidence of severe blood loss compared with the ACT approach.

9.1.2.2. Protamine

A recent double-blind RCT investigated the effect of basing protamine dosages on protamine–heparin titrations in valve replacement patients ($n = 60$).[204] The authors found that basing protamine measurements on two separate protamine–heparin titrations, the first at termination of CPB and the second five minutes after the first dose of protamine, can reduce postoperative blood loss by reducing protamine–heparin mismatch.

9.1.2.3. Antifibrinolytic therapy (tranexamic acid and ε-aminocaproic acid)

Recent studies have shown varying results. One retrospective study compared aprotinin to EACA in a consecutive infant patient population ($n = 227$) undergoing cardiac surgery requiring CPB.[205] Chest-tube output was significantly higher in the EACA group, although this did not affect transfusion requirements. Sensitivity analysis revealed lower efficacy with EACA compared with aprotinin. A prospective randomised study in a consecutive group of adults ($n = 64$) undergoing thoracic aortic surgery requiring CPB found that both EACA and tranexamic acid were effective in reducing postoperative blood loss.[206] However, EACA significantly increased

the risk of renal injury and failure, whereas tranexamic acid increased the risk of seizures.

Evidence of the benefits of tranexamic acid is less clear-cut in paediatric versus adult cardiovascular surgery. A systematic review and meta-analysis of eight studies ($n = 848$) concluded that while there was a small reduction in blood transfusions across the population that were administered tranexamic acid, the quality of the evidence was weak and much of it was too heterogeneous to be analysed in the meta-analysis.[207]

Not all studies have shown positive results. One prospective, double-blind, randomised, placebo-controlled clinical trial ($n = 90$) compared tranexamic acid with low-dose aprotinin and a control in adult cardiac valve surgery patients.[208] The chest drain output was significantly lower in the aprotinin group; the quantity of RBC and platelet transfusions was significantly lower in the aprotinin and tranexamic acid groups compared with the control; and the quantity of FFP transfusion was significantly lower only in the aprotinin group. The authors concluded that low-dose aprotinin was superior to tranexamic acid in reducing blood loss.

A prospective clinical trial ($n = 1182$) investigated the efficacy of giving small and medium 'single shots' of tranexamic acid in CPB priming volume (1 g and 5 g, respectively), and a medium dose (3 g)plus 15 mg kg^{-1} h^{-1}) infusion in elective cardiac surgical patients.[209] The trial found no significant differences between the groups in postoperative blood loss, and the authors concluded that the higher doses were no more effective than the single low dose of tranexamic acid.

Several randomised studies have compared high and low continuous doses of tranexamic acid during surgery. A prospective, randomised, double-blind trial ($n = 175$) in cardiac valve surgery patients compared tranexamic acid at a 'low' dosage which consisted of a loading dose of 10 mg kg^{-1}, followed by a maintenance dose of 2 mg kg^{-1} h^{-1}, and a CPB prime of 40 mg; to a 'high' dosage which consisted of a loading dose of 30 mg kg^{-1}, maintenance dose of 16 mg kg^{-1} h^{-1}, followed by a CPB prime of 2 mg kg^{-1}.[210] The study found that the lower dose was as effective as the higher dose in preventing postoperative bleeding. A multi-centre, double-blinded, randomised, controlled study ($n = 568$) compared a 'low' dose (10 mg kg^{-1} loading dose followed by maintenance with 1 mg kg^{-1} h^{-1} until the end of the operation) with a 'high' dose (30 mg kg^{-1} loading dose followed by maintenance with 16 mg kg^{-1} h^{-1}).[211] The results showed no significant difference between the two doses in the incidence of overall transfusions up to 7 days post-surgery, but the higher dose did reduce blood loss, the need for transfusions, and further surgery. A small double-blind, randomised, controlled pilot trial ($n = 33$) compared a 'low' dose, consisting of a loading dose of 5 mg kg^{-1} followed by a maintenance dose of 5 mg kg^{-1} h^{-1}; a 'high' dose consisting of a bolus of 30 mg kg^{-1} and a maintenance dose of 16 mg kg^{-1} h^{-1}; and a sodium chloride control.[212] The study found no differences in bleeding outcome or fibrinolysis between any of the three groups.

Tranexamic acid may also be used topically. A meta-analysis of four randomised, double-blind, controlled trials ($n = 371$) on topical tranexamic acid use in cardiac surgery found a significant reduction in 24-h postoperative blood loss, but could not prove a significant reduction in transfusion.[213] A more recent prospective, double-blind, clinical trial ($n = 71$) found similar results, with a significant reduction in blood loss; there was also a non-significant reduction in RBC transfusion, but no significant difference in blood component transfusion.[214] One retrospective cohort study ($n = 160$) examined the effects of using combined intravenous and topical tranexamic acid doses compared with an intravenous tranexamic acid regimen in CABG patients.[215] Blood loss was significantly decreased at 3, 6 and 12 h postoperatively in the combined dose group: the authors recommend further RCTs in this area.

In a recent prospective, double-blind, placebo-controlled, randomised clinical trial ($n = 231$), adult patients undergoing off-pump CABG were treated with either a 1 g bolus of tranexamic acid followed by 400 mg h^{-1} during surgery, or a sodium chloride placebo.[216] The results showed significant reductions in post-surgical chest-drain volume at 6 h, and in transfusion requirements for RBC and FFP, compared with the control group. One study has assessed the use of EACA as a topical treatment intraoperatively in off-pump cardiac surgery. The study was a prospective, double-blind, RCT ($n = 26$) which compared topical EACA with a placebo; there were no significant differences in blood loss or transfusion requirements.[217]

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

One small, prospective study ($n = 13$) reported that cryoprecipitate increased fibrinogen levels and fibrin-based clot strength in aortic surgery patients undergoing deep hypothermic circulatory arrest.[218]

A recent prospective, cohort study named PLASMACARD ($n = 967$), concluded that FFP usage in cardiac surgery has no beneficial impact on 30-day mortality rates.[219] Evidence from another study, a retrospective analysis of 685 patients, suggests that using autologous platelet-rich plasma may be an effective haemostatic option in thoracic aortic surgery. Significantly reduced allogeneic blood transfusions were reported, together with a decrease in major adverse events among patients receiving autologous platelet-rich plasma, compared with controls.[220] However, a large RCT is needed to confirm

the efficacy of autologous platelet-rich plasma as a haemostatic option.

9.1.2.5. Desmopressin

A recent double-blind RCT ($n = 102$) tested the effects of DDAVP on postoperative blood loss and platelet aggregation.[221] The intervention group was treated with 0.3 $\mu g\,kg^{-1}$ during surgery and a control group received saline. The results showed a significant decrease in postoperative blood loss and FFP transfusions in the DDAVP group during the first 6 h post-surgery (the duration of drug activity). However, by 24 h there was no significant difference between the groups. No effects on platelet aggregation, RBC or platelet transfusion were observed.

9.1.2.6. Coagulation factor replacement therapy

9.1.2.6.1. Factor XIII concentrate

A recent double-blind, placebo-controlled, multi-centre trial ($n = 409$) investigated whether replenishing factor XIII levels has an effect on postoperative transfusion rates in CPB patients.[222] No effect on transfusion avoidance, transfusion requirements or surgical re-exploration was observed.

9.1.2.6.2. Fibrinogen concentrate

A secondary analysis of data from a randomised, double-blind, placebo-controlled trial performed in patients undergoing complex cardiovascular surgery ($n = 61$) investigated the effect of FIBTEM-guided fibrinogen supplementation on the rate of intraoperative bleeding.[223] It was found that fibrinogen concentrate was more effective than placebo or one cycle of transfusion with FFP and platelets in reducing the rate of bleeding.

Fibrinogen concentrate has also been compared with cryoprecipitate in a randomised study ($n = 63$) performed in bleeding paediatric cardiac surgery patients with low fibrinogen levels after CPB.[224] The results showed no significant differences between the agents, and the authors concluded that fibrinogen was as well tolerated and effective as cryoprecipitate in controlling blood loss up to 48 h postoperatively. Not all studies have shown favourable results with fibrinogen concentrate use. One large, retrospective cohort analysis ($n = 1075$) of non-randomised fibrinogen intervention in complex cardiac surgery found no effect on blood loss or transfusion rate, but no increased risk of adverse events.[225] The authors concluded that the low dose and late administration may have affected the results, and have initiated an RCT to investigate further.

9.1.2.6.3. Prothrombin complex concentrate

A small, prospective study ($n = 14$) using a bolus of commercially available PCC found it was effective at reducing postoperative bleeding and RBC transfusions in paediatric cardiac surgery patients.[226] Another prospective study performed in cardiac surgery patients ($n = 25$) investigated a PCC containing small amounts of factor VIIa and found it to significantly reduce the need for FFP and platelet transfusions.[227] One retrospective study ($n = 168$) has compared the efficacy of FEIBA and rFVIIa.[228] No significant difference was found between the two procoagulants in terms of morbidity and mortality. Platelet transfusion was higher among patients receiving rFVIIa, but no other differences in transfusion requirements were identified.

9.1.2.6.4. Recombinant activated factor VII

A recent RCT, conducted to compare a group of CABG patients receiving rFVIIa after weaning from CPB ($n = 30$) with a control group, found significant decreases in chest drain output and transfusion requirements in the intervention group.[229] The authors highlighted the need for more larger-scale RCTs. Research into dosing has progressed very little, but one retrospective study ($n = 69$) has compared dosing and efficacy between adult and paediatric patients, with intraoperative and postoperative treatment.[230] Prophylactic therapy tended to be more effective, and adults benefited from a much smaller dose per kilogram of body mass than children, due to the shorter half-life of the factor in children.

Although rFVIIa is efficacious in reducing perioperative bleeding, a limited body of research suggests that rFVIIa might increase morbidity and mortality. A single-centre, retrospective review ($n = 16$) of paediatric patients who received rFVIIa intraoperatively or postoperatively found a 56% mortality rate, attributed to neurological, bleeding and septic events.[231] In an observational case control study with patients who received rFVIIa ($n = 144$) intraoperatively or postoperatively and matched controls ($n = 359$), the in-hospital mortality was 40% in the group receiving rFVIIa and 18% in the control group.[232] Renal morbidity was also increased in the group receiving rFVIIa (31 versus 17%, respectively).

9.1.2.6.5. Antithrombin

A review[56] comparing antithrombin with FFP for the treatment of patients with heparin resistance found a lower risk of TRALI, superior efficacy and a lower volume of administration with antithrombin. However, there was a paucity of good quality evidence with only three case reports, one RCT and one retrospective analysis.

9.1.2.6.6. Factor IX

A retrospective study of 11 patients receiving 35 $\mu g\,kg^{-1}$ versus controls showed that factor IX produced a significant reduction in chest tube drainage, but it had no significant effect on blood product usage.[233]

9.1.2.7. Fibrin sealant (fibrin glue)

A recent non-randomised, prospective study ($n = 42$) compared the haemostatic efficacy of a surgical patch

containing thrombin and fibrinogen with a conventional treatment control in patients undergoing cardiothoracic surgery.[234] The authors observed reduced RBC transfusions in the intervention group compared with the control group, but there was no reduction in intraoperative or postoperative blood loss.

9.1.3. Which therapies influence bleeding in the postoperative period?

Recommendation

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**

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

Recommendation

We recommend the use of standardised VHA-guided haemostatic algorithms with pre-defined intervention triggers. **1B**

The most recent systematic review of 12 studies ($n = 6835$), observed a reduction in transfusion requirements in patients managed by TEG-guided or ROTEM-guided therapy.[48] Transfusion of FFP, platelets and RBC were all reduced; this may have been due to TEG-/ROTEM-guided therapy being more restrictive than control therapy, or control therapy being too liberal. The authors concluded that evidence for the use of TEG-guided/ROTEM-guided intervention algorithms is still lacking.

Two recent RCTs, published in 2015, have also found that preoperative and intraoperative point-of-care testing can reduce transfusion requirements. One RCT ($n = 249$) was conducted in patients undergoing CABG surgery.[235] Preoperative platelet function testing was used in a control group and two intervention groups: one tested using multiple electrode aggregometry and the other using TEG Platelet Mapping. The results showed a significant reduction in blood product transfusions in the intervention groups compared with the control. The authors also reported a greater effect in patients who had been treated with an ADP-receptor antagonist within 5 days before undergoing surgery. The other RCT, conducted in paediatric patients ($n = 100$), found that intraoperative ROTEM-guided therapy (EXTEM A10 and FIBTEM A10) post-CPB significantly reduced postoperative blood loss and RBC transfusion, both postoperatively and throughout intensive care stay.[41] In addition to these RCTs, two recent observational studies have demonstrated significant reductions in transfusion requirements after implementation of a blood product utilisation algorithm and a point-of-care monitoring-based intervention algorithm, respectively.[236,237]

9.2. Gynaecological (non-pregnant) surgery

9.2.1. Treatment of perioperative anaemia

9.2.1.1. Minimising gynaecological RBC transfusion

Recommendation

We suggest that normovolaemic haemodilution should not be used as it does not reduce allogeneic transfusion. **2B**

9.2.1.2. Should cell salvage be used in gynaecological surgery?

Recommendation

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

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

Recommendations

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

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

9.2.2. Coagulation monitoring and treatment

9.2.2.1. What are the indications for antifibrinolytics (tranexamic acid)?

Recommendation

Tranexamic acid may reduce perioperative bleeding in gynaecological cancer surgery. **C**

9.3. Obstetric bleeding

9.3.1. Treatment of postpartum anaemia

Anaemia develops in up to 29% of pregnancies in the third trimester.[238] Peripartum bleeding is the major risk factor for severe postpartum anaemia[239] but peripartum transfusions may complicate delivery.[240–242] Here, we assess whether correction of anaemia is required as part of treating obstetrical haemorrhage and the therapeutic options available.

Related topics of PPH such as diagnosis of PPH, treatment of uterine atony, retained placental tissue, arterial embolisation and others are beyond the scope of this guideline. We recommend other evidence-based clinical guidelines such as the WHO guidelines for the management of PPH and retained placenta.[243]

9.3.1.1. Obstetric triggers for red blood cell transfusion

Recommendations

We recommend that PPH should be managed by a multidisciplinary team. **1C**

We recommended the use of an escalating PPH management protocol including uterotonic drugs, surgical and/or endovascular interventions, and procoagulant drugs. **1B**

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

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

9.3.1.2. 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**

9.3.1.3. Intravenous iron or erythropoietin in the treatment of postpartum anaemia

Recommendation

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

PPH should be treated promptly. Delayed recognition of and response to acute bleeding is a leading cause of maternal mortality and 'near misses'.[244] A protocol-based intervention grants an early access to blood products.[245,246] Suboptimal Hct during the acute phase of PPH is associated with end organ dysfunction.[247,248]

Blood transfusions have increased substantially in the last decade.[249] Although no clinical studies of transfusion trigger Hb thresholds in life-threatening obstetric haemorrhage were retrieved, a general observance of an Hb threshold of 8.1 g dl^{-1}, to ensure a haemoglobin level of 7 to 8 g dl^{-1}, has been reported.[250] However, in a study of French maternity units, it was reported that RBC transfusion for PPH was not given in a large proportion of women with very low haemoglobin levels.[251]

Haemoglobin levels and health-related quality-of-life physical fatigue scores correlate in the first week postpartum. Nevertheless, transfusion in patients with low haemoglobin concentration without clinical signs of anaemia has little effect on physical fatigue.[252,253] In this context, a restrictive strategy (haemoglobin threshold: 7 g dl^{-1}) seems equally well tolerated and justified.

9.3.1.4. Should cell salvage be used in obstetrics?

Perioperative cell salvage has been used in obstetric surgery but is not widely established due to technology issues and a lack of staff training.[254] In obstetric haemorrhage, the routine use of cell salvage is associated with more salvaged blood returned to the patients, and the costs may be partly offset by reduced allogeneic blood use.[255]

9.3.1.5. Intravenous iron or erythropoietin in the treatment of postpartum anaemia

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, which elicits more rapid recovery from shorter treatment compared with oral therapy.[256]

9.3.2. Peripartum haemorrhage: coagulation monitoring and management

9.3.2.1. Fibrinogen measurement

Recommendation

We suggest assessing fibrinogen levels in parturients with bleeding, as levels less than 2 g l^{-1} may identify those at risk of severe PPH. **2B**

Fibrinogen levels decrease with increasing blood loss and may serve as a marker of haemostatic impairment.[257,258] Functional markers of fibrinogen such as FIBTEM MCF and FIBTEM A5 seem to be equally associated with morbidity and the need for transfusion during PPH.[259,260] However, it is not known whether a low fibrinogen level per se, or a low fibrin-based clot firmness, causes progression of PPH or reflects the severity of the bleed and the resuscitation effort required.[259] Evaluation of fibrinogen at the onset of labour is of less predictive value.[261,262] Fibrinogen concentration is correlated with estimated blood loss, kaolin-TEG maximum amplitude,[263,264] FIBTEM MCF and FIBTEM A5.[265]

9.3.2.2. Platelet count

Recommendation

Dynamic platelet count decrease or a level less than 100×10^9 l^{-1} at the onset of labour, particularly if combined with plasma fibrinogen level less than 2.9 g l^{-1}, may indicate an increased risk of PPH. **C**

Low platelet count is associated with increased RBC and FFP transfusion.[266] When blood loss reaches 2000 ml, platelet count is significantly reduced.[263]

9.3.2.3. Activated partial thromboplastin time and prothrombin time

Recommendation

At the beginning of labour aPTT and PT are of little predictive value for PPH. **C**

aPTT and PT show a small but significant correlation with estimated blood loss in PPH.[267,268]

9.3.2.4. Viscoelastic haemostatic assays

Recommendation

VHA can identify obstetric coagulopathy. **B**

VHAs provide results in 5 to 15 min and are faster than SLTs.[264] FIBTEM, a bedside thromboelastometric fibrin-clot quality test, can indicate a reduced contribution of fibrinogen to clot strength.[269,270] FIBTEM maximum clot firmness is significantly decreased during PPH.[270,271]

Kaolin-TEG maximum amplitude is correlated with estimated blood loss and fibrinogen concentration.[263,264] When blood loss reaches 2000 ml, TEG shows decreased maximum amplitude, decreased clot initiation (prolonged r-time) and reduced fibrinolytic activity (LY30%).[263,264]

Thromboelastometric measurements can identify the hypercoagulability seen in normal pregnancy,[272,273] in caesarean section,[274,275] and in pre-eclampsia and HELLP syndromes, as well as cases of impaired haemostasis due to other causes.[276] These measurements can allow rapid recognition of hyperfibrinolysis and guide therapy with tranexamic acid, fibrinogen concentrate, PCC, FFP and platelets.[263]

9.3.2.5. Hyperfibrinolysis

Split products of fibrin (D-dimer) may increase during PPH,[277] but there is little evidence of hyperfibrinolysis in severe PPH versus non-severe PPH.[263]

9.3.3. Haemostatic treatment of obstetric haemorrhage

Transfusion of FFP, platelets and cryoprecipitate may be a marker for bleeding severity and volume of RBCs required.[278] An algorithm for managing obstetric haemorrhage[279] suggests transfusion with FFP if INR is more than 1.5, with platelets if platelet count is less than 25×10^9 l^{-1}, and with cryoprecipitate if fibrinogen is less than 100 mg dl^{-1}. A high RBC:FFP ratio is associated with lower risk of advanced interventional procedures to arrest the postpartum bleeding.[280]

Pregnancy-related hypertensive disorders seem to increase the risk of TRALI in patients in need of postpartum blood transfusions.[281,282]

9.3.3.1. What are the indications for fibrinogen replacement with fibrinogen concentrate or cryoprecipitate?

We recommend against pre-emptive fibrinogen replacement; however, in ongoing PPH with hypofibrinogenaemia we recommend fibrinogen replacement. **1C**

Fibrinogen levels are typically elevated (approximately 5 g l^{-1}) in pregnancy; however, we are currently unaware whether trigger levels above 1.5 to 2 g l^{-1} should be applied in obstetrics.[283–285] Fibrinogen functionality might be impaired by dilution, local or disseminated consumption.[286] The underlying obstetrical cause of bleeding should guide the clinical suspicion of impaired haemostasis.[287] Trigger levels for fibrinogen substitution vary between 1 and 2 g l^{-1} and FIBTEM A5 less than 12 mm, with a mean administered dose of 2 to 4 g.[265,284,288] One retrospective study suggests that fibrinogen concentrate is equally efficacious in treating hypofibrinogenaemia compared with cryoprecipitate but seems faster to use.[289,290]

In an RCT involving patients with postpartum haemorrhage, a mean estimated blood loss of 1500 ml and normofibrinogenaemia found no benefit of early pre-emptive treatment with 2 g of fibrinogen concentrate compared with placebo.[285,291] FIBTEM-guided fibrinogen substitution might improve patient outcomes.[288,292]

No serious adverse events were reported with fibrinogen concentrate in the obstetric setting.[285]

9.3.3.2. Guiding therapy in obstetric bleeding

Recommendation

In severe PPH we suggest a VHA-guided intervention protocol. **2C**

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

Recommendations

We suggest that tranexamic acid be considered before caesarean section and in cases of antepartum bleeding. **2B**

We recommend the administration of tranexamic acid in PPH at a dose of 1 g IV as soon as possible, which can be repeated if bleeding continues. **1B**

Fibrinolysis is decreased during pregnancy[263,264]; however, abnormal fibrinolysis is associated with complications, for example placental abruption with antepartum bleeding.[293]

Antifibrinolytic therapy, used prophylactically for vaginal[294] or caesarean delivery, or when postpartum bleeding evolves,[295] may prevent such complications. A recent RCT found that tranexamic acid administered before caesarean section may reduce perioperative blood loss.[296]

Tranexamic acid reduces blood loss, bleeding duration and possibly transfusion requirements in PPH.[297–300] In a recent meta-analysis, only a few trials observed adverse events including thromboembolic complications and seizures; gastrointestinal adverse events were more common in those patients receiving tranexamic acid compared with placebo.[300]

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

In two cases of amniotic fluid embolism, sufficient haemostasis was achieved by thromboelastometric-guided coagulation therapy comprising tranexamic acid, fibrinogen concentrate, platelets and PCC, as well as RBC and FFP in a 1 : 1 ratio, and rFVIIa.[301]

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

rFVIIa can be considered as second-line haemostatic therapy alongside intrauterine tamponade, uterine compression sutures, pelvic vessel ligation and interventional

radiology.[302] Case reports[303–305] and retrospective studies[302,306–309] support off-label use of rFVIIa for severe obstetric coagulopathic bleeding.

An RCT showed reduced need for interventional second-line therapies following administration of 60 μg rFVIIa for postpartum haemorrhage, but also increased risk of thromboembolism in 1 of 20 patients.[310]

9.4. Orthopaedic surgery and neurosurgery

9.4.1. Bleeding risk due to pre-existing coagulation disorders and medications

Elective orthopaedic surgery following the implantation of a coronary stent could result in a prohaemostatic condition and increases the risk of stent thrombosis. To minimise this thrombotic risk, elective orthopaedic surgery should be postponed for a minimum of 4 weeks and optimally for up to 3 months after BMS implantation and up to 12 months after DES implantation.[311,312]

9.4.2. Screening tests to predict bleeding in orthopaedics and neurosurgery

Recommendations

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

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

9.4.3. Antifibrinolytics

There is growing evidence for the well tolerated and beneficial use of tranexamic acid to reduce perioperative blood loss, allogeneic blood transfusions and associated costs in major orthopaedic surgery such as total hip or knee arthroplasty, and spine surgery.[313–326]

However, tranexamic acid is not recommended in patients with hypersensitivity or allergy to the drug, history of venous or arterial thrombosis, or thrombophilia, cardiovascular disease, acute renal failure or subarachnoid haemorrhage, or in patients with a history of seizures or epilepsy.[327]

There is emerging evidence that topical administration of tranexamic acid may be beneficial in reducing the rate of blood transfusions in both total hip replacement and total knee replacement surgery.[315,328–333]

9.4.4. Prothrombin complex concentrate and non-vitamin K-dependent oral anticoagulants

For life-threatening bleeding or ICH among oral anticoagulation patients receiving VKAs, with INR more than 1.5, guidelines recommend the administration of four-factor PCCs over FFP or rFVIIa for immediate reversal of INR, with co-administration of vitamin K (5 to 10 mg by slow intravenous infusion).[334–338] In general, initial PCC doses for emergency VKA reversal in life-threatening bleeding range between 25 and 50 IU kg^{-1}.[338]

In comparison with other reversal strategies, four-factor PCCs provide quicker and more controlled correction of INR and improved bleeding control than FFP, with a favourable safety profile.[339–344]

Because thromboembolic events after the administration of PCC have been related to high doses, it is advisable that the repeated administration of PCC should be guided by the effect on the INR: if INR is less than 1.5 we suggest not administering another dose of PCC, although clinical parameters should also be assessed.[345]

Activated PCCs are not indicated for the reversal of VKA-induced anticoagulation even in emergency bleeding situations. Their use should be restricted to patients with haemophilia A and B with inhibitors to coagulation factors VIII or IX for control and prevention of bleeding episodes, perioperative management or routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ICH is a medical emergency. Quick diagnosis and management of ICH to limit its expansion is of primary importance because clinical deterioration is common in the first few hours after ICH onset. Patients on VKA anticoagulation are at risk of ICH, with worse outcomes than non-anticoagulated patients.[346] The poorer outcomes are mainly related to the volume of the initial haemorrhage and its speed of growth. The general recommendation is to reverse the VKA anticoagulation as rapidly as possible.

PCCs are preferable to FFP for rapidly reversing INR, improving haemostasis and increasing levels of vitamin-K dependent coagulation factors in patients requiring urgent restoration of haemostasis.[347,348]

DOACs (dabigatran, rivaroxaban, apixaban or edoxaban) may increase surgical bleeding. In orthopaedic surgery they are indicated as thromboprophylaxis in selected procedures (total hip or knee arthroplasty), with administration in the early postoperative period.

Although some antidotes are in the advanced stages of development,[349,350] they are not generally available for routine clinical use. Four-factor PCC, activated PCC and rFVIIa have all been investigated for reversing the anticoagulant actions of DOACs.[351–354] However, there is limited evidence that these agents provide clinical benefit, and a definite lack of evidence regarding optimal dosing and possible thrombotic risk. In some animal models and *ex vivo* studies, the administration of such haemostatic agents has been demonstrated to improve coagulation parameters and/or decrease haemorrhage.[351,355–362] In cases of life-threatening bleeding or ICH, it is unclear whether the administration of these powerful haemostatic agents would be effective in

clinical practice[363–365] because the correction of haemostatic laboratory parameters does not necessarily correlate with bleeding control.[349] Another option in bleeding patients under the effect of dabigatran is haemodialysis.[365,366]

9.5. Paediatric surgery

9.5.1. Coagulation monitoring

Recommendation

We suggest low-volume sampling for standard coagulation tests and VHA-guided interventions. **2C**

There is growing evidence to support the use of VHA-guided paediatric coagulation management, including three RCTs.[41,51,212,367–378] In children undergoing cardiac surgery, Nakayama *et al.*[41] randomised 100 children to be treated using a ROTEM-guided algorithm or a routine approach based on standard coagulation assays. The utilisation of a ROTEM-guided approach significantly reduced chest tube drainage output measured at 12 and 24 h postoperatively. Although no difference in the total amount of blood products transfused was observed, the ROTEM-guided algorithm was associated with increased intraoperative blood products transfusion, and a decrease in postoperative transfusion. These results confirmed that the use of ROTEM-guided algorithm allows for an earlier treatment of coagulopathy, leading to decreased postoperative bleeding.

9.5.2. Fluid resuscitation

Recommendation

We recommend the use of isotonic and balanced resuscitation fluids in bleeding children. **1C**

Recent studies suggest that intraoperative positive fluid balance could contribute to postoperative fluid overload, which has been shown to significantly affect patient outcome.[379–381] Although most of these studies were performed in children undergoing cardiac surgery, fluid overload should be avoided in all clinical contexts; fluid administration and balance should be monitored carefully.

9.5.3. Red blood cell transfusion

Recommendation

Except for premature babies and cyanotic newborns, haemoglobin targets in bleeding children are 7 to 9 g dl^{-1}. **C**

9.5.4. Coagulation factor concentrates

9.5.4.1. Fibrinogen concentrate

Intraoperative administration of fibrinogen concentrate (50 mg kg^{-1}) has been used effectively to treat hypofibrinogenaemia (ROTEM FIBTEM maximum clot firmness $\leq$7 mm) during major paediatric surgery.[367,372,378] However, neither the optimal threshold for initiation of fibrinogen replacement nor the dose required to reach the targeted fibrinogen concentration, have been proven by high-quality data.

FFP may not provide an adequate increase in plasma fibrinogen concentrations, and a minimum volume of 20 to 30 ml kg^{-1} should be administered before expecting a significant increase in fibrinogen concentration.[382] No study has assessed the response observed in fibrinogen concentration after the administration of FFP in children.

9.5.4.2. Antifibrinolytics

Based on tranexamic acid pharmacokinetic data, a loading dose of 10 mg kg^{-1} over 15 min followed by a 5 mg kg^{-1} h^{-1} maintenance infusion may be sufficient to maintain adequate plasma concentrations during craniosynostosis surgery.[383] However, further RCTs are needed to assess the efficacy of this dose regimen. In a recent comprehensive pharmacokinetic study performed in neonates and children undergoing cardiac surgery, different dose schemes based on patients' ages and the targeted plasma concentration were recommended.[384] As the minimum plasma concentration required to completely inhibit fibrinolysis in different surgical settings is not known, further studies are needed before we can recommend the optimal dosing schemes based on pharmacokinetics and pharmacodynamics.[385]

9.6. Visceral and transplant surgery

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

9.6.1.1. What is the evidence that haemostasis is 're-balanced' in chronic liver disease?

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

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

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

9.6.2. 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**

9.6.3. Orthotopic liver transplantation

9.6.3.1. Intraoperative fluid management

Recommendations

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

We recommend a low CVP and restrictive fluid administration during liver surgery to reduce bleeding. **1B**

Maintenance of low CVP during hepatic resection reduces blood loss and transfusion requirements.[386,387] Low transfusion rates (<80%) during OLT have been reported using fluid restriction, phlebotomy, vasopressors and transfusion protocols.[388]

9.6.4. Coagulation monitoring

Conventional coagulation tests do not reliably predict bleeding,[389] nor does an elevated INR exclude hypercoagulability.[390]

9.6.4.1. Global coagulation tests: thrombelastography/thromboelastometry

Other evidence suggests TEG/ROTEM monitoring may help reduce bleeding and transfusion of FFP and platelets in liver transplantation.[391,392]

9.6.5. Pharmacological therapy

9.6.5.1. Antifibrinolytic drugs

Recommendations

We recommend tranexamic acid for treatment of fibrinolysis (evident from microvascular oozing or VHA clot lysis measurement) but not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis post-reperfusion. **1C**

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

A treatment strategy of administering antifibrinolytic therapy based on the presence of fibrinolysis on viscoelastic testing does not appear to result in increased bleeding compared with a prophylactic regime.[393]

9.6.6. Acute upper gastrointestinal bleeding

A large multi-centre trial (HALT-IT) of the efficacy and safety of tranexamic acid is in progress.[394]

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**

TIPSS can be suggested as an option for rescue therapy after initial medical and endoscopic therapy fail. **2B**

We recommend early interventional endoscopy and the immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding. **1B**

Tranexamic acid reduces mortality but not re-bleeding. **B**

In a systematic review it has been shown that TIPSS can reduce failure to control bleeding and re-bleeding, as well as mortality.[395] In high-risk cirrhotic patients, an RCT also demonstrated that early use of TIPSS is associated with a significant reduction in treatment failure and mortality.[396]

9.6.6.1. Fluid resuscitation and pharmacological interventions

A single-centre study of over 900 patients randomised to a restrictive (70 g l^{-1}) or liberal (90 g l^{-1}) transfusion strategy demonstrated that the risks of death and re-bleeding were lower with the restrictive threshold.[126] However, the study was unblinded and no subgroup analysis for coronary artery disease was performed. Another single-centre RCT with 921 patients, found that a restrictive transfusion strategy significantly improved outcomes compared with a liberal transfusion strategy.[397] A large cluster, randomised feasibility study performed in six UK centres demonstrated decreased transfusions with restrictive (80 g l^{-1}) compared with liberal (100 g l^{-1}) strategies, but no differences in patient outcomes were observed.[398] It is too early for these studies to inform clinical practice directly, as the safety of low transfusion thresholds in patients with ischaemic heart disease remains a key area of uncertainty. However, two recently published guidelines both recommend that a restrictive transfusion threshold of 70 to 80 g l^{-1} should be used.[399,400]

9.6.7. Coagulopathy and renal disease

9.6.7.1. Assessment of platelet function

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**

PFA-100 is not useful for the prediction of bleeding complications.[401]

9.6.7.2. Correction of bleeding diathesis and treatment of bleeding

Recommendations

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

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

DDAVP can treat platelet dysfunction in uraemic patients. DDAVP induces VWF release, improving platelet adhesion/aggregation, and has been shown to be effective for both prophylaxis and the treatment of perioperative bleeding.[402,403] However, it can cause significant dilutional hyponatraemia.[404]

10. Antithrombotic drugs

10.1. Introduction

Antithrombotic therapies have a range of indications, and in this section we describe how they are managed in anaesthesia and intensive care.

10.2. Antiplatelet agents

Perioperative interruption and maintenance of APAs are associated with increased thrombotic or haemorrhagic complications, respectively. Recommendations for perioperative APA therapy are based on only one large controlled study, along with small observational studies, case reports and expert opinion, so most recommendations are weak. In patients with coronary stents, interruption of APA is a risk factor for stent thrombosis. 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.

10.2.1. Aspirin

Recommendations

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

Where aspirin withdrawal before surgery is considered, we recommend a time interval of 3 days. **1C**

In patients with risk factors for vascular complications naïve of any antiplatelet treatment, it is not recommended that treatment with aspirin be initiated preoperatively. **1B**

In patients treated chronically with aspirin for the secondary prevention of cardiovascular events, except those patients with coronary stents, we recommend aspirin interruption for procedures where there is a very high bleeding risk. **1B**

In patients chronically treated with aspirin for secondary prevention of cardiovascular events, we recommend aspirin be maintained during and after low and medium bleeding risk procedures. **1B**

We suggest careful consideration of postoperative bleeding complications when timing the first postoperative administration and dose of anticoagulants along with resumption of aspirin. **2C**

For intraoperative or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7×10^{11} per 10 kg body weight in adults). **2C**

We recommend that aspirin be continued for at least 4 weeks after BMS implantation and 3 to 12 months after DES implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high. **1A**

Treatment discontinuation increases thrombotic risk. Following aspirin withdrawal, aspirin treatment should resume as soon as possible postoperatively to prevent platelet activation. A risk of surgical bleeding is also associated with APA therapy; however, this has been poorly evaluated.

In a large RCT, POISE 2, patients undergoing non-cardiac surgery were randomised to receive aspirin or placebo before and after surgery.[405] Using a 2-by-2 factorial trial design (exploring also the efficacy and safety of clonidine to prevent cardiovascular events), 10 010 patients at risk of vascular complications and who were undergoing non-cardiac surgery were included. The patients were stratified according to whether they had not been taking aspirin before the study (aspirin initiation group, 5628 patients) or they were already on an aspirin regimen (aspirin continuation group, 4382 patients). Patients in the continuation group stopped their usual aspirin 3 days before surgery. Then all started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it daily (at a dose of 100 mg) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. The primary outcome, a composite of death or non-fatal myocardial infarction at 30 days, occurred in 7.0% of patients in the aspirin group and in 7.1% of patients in the placebo group ($P = 0.92$). Major bleeding was more common in the aspirin group than in the placebo group [230 patients (4.6%) versus 188 patients (3.8%); hazard ratio, 1.23; 95% CI, 1.01 to 1.49; $P = 0.04$]. A majority of patients included in this study had only risk factors for perioperative cardiovascular events including a majority of aged or hypertensive and/or diabetic patients. Less than 35% of patients had a history of vascular disease. The majority of patients were Revised Cardiac Score Index 1. As a result, most patients included in the initiation group would not have been otherwise treated by aspirin.

Major bleeding was significantly higher in the aspirin group; however, this was significant only in the initiation group. An interaction between antiplatelet and postoperative anticoagulant therapy may explain a higher major bleeding rate in the aspirin group. In addition, a lack of antithrombotic efficacy of aspirin was observed but, as the postoperative use of NSAIDs was allowed (>40% of the patients), this may have interfered with aspirin efficacy by blocking access to the COX-inhibitor pathway.

In summary, aspirin should not be withdrawn perioperatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug.

10.2.2. P2Y12 receptor inhibitors: clopidogrel, prasugrel and ticagrelor

Recommendations

We suggest that P2Y12 inhibitor treatment be considered for at least 4 weeks after BMS implantation and 3 to 12 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high. **2A**

If clinically feasible, we suggest postponing (semi-urgent) surgery for at least 5 days after cessation of ticagrelor and clopidogrel, and for 7 days in the case of prasugrel, unless the patient is at high risk of an ischaemic event. **2B**

We recommend that APA 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 that a multidisciplinary team meeting should decide on the perioperative use of APAs 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 be considered (dose: 0.7×10^{11} per 10 kg body weight in adults) in cases of intraoperative 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 transfusions may be ineffective for treating bleeding related to ticagrelor if given within 12 h of the drug's administration. **C**

In a systematic review of 37 studies (31 cardiac and six non-cardiac surgery; three randomised, 34 observational), postoperative outcomes in patients who were or were not exposed to thienopyridine in the 5 days before surgery were compared.[406] Exposure to thienopyridine in the 5 days preceding surgery (compared with no exposure) was not associated with any reduction in postoperative myocardial infarction, but was associated with increased risks of stroke, re-operation for bleeding and all-cause mortality. Results were similar when analyses were restricted to long-term users of thienopyridines who continued versus those who withheld the medication in the 5 days before surgery. Although all associations were similar for the subset of patients undergoing non-cardiac surgery, 97% of the outcome data in this meta-analysis came from cardiac surgery trials.

A large phase 3 study (TRITON-TIMI 38) compared prasugrel with clopidogrel in patients with acute coronary syndrome (ACS) scheduled to undergo percutaneous coronary intervention. In a subset of patients requiring CABG, platelet transfusions were administered to significantly more patients, and at a significantly higher dose, in patients in the prasugrel arm than in patients allocated to the clopidogrel arm.[407] Platelet aggregation recovery period after prasugrel interruption took longer than after clopidogrel interruption.[408] This antiplatelet effect lasts for the lifespan of the platelets ($\geq$7 days). Recommendations for clopidogrel should be applicable to prasugrel, except for the duration of withdrawal (7 days of interruption for prasugrel).

No studies on efficacy of platelet transfusion in patients treated with ticagrelor were retrieved. However, when ticagrelor is administered within the preceding 12 h, its presence in plasma may render platelet transfusion ineffective.[409]

10.2.3. Dual antiplatelet therapy

The prognosis of stent thrombosis appears to be worse than for *de novo* coronary occlusion, and premature cessation of dual antiplatelet therapy (DAPT) in patients with recent coronary stent implantation is the most powerful predictor for stent thrombosis. The management of antiplatelet therapy in patients who have undergone recent coronary artery stent treatment, and are scheduled for non-cardiac surgery, should be discussed to balance the risk of procedural bleeding on antiplatelet therapy and the risk of MACE, including stent thrombosis. Most studies exploring the risk of stent thrombosis following DAPT interruption have been performed in patients implanted with first-generation stents. Duration of DAPT for these first-generation stents was 12 months. Recent publications from new-generation DES (zotarolimus-eluting and everolimus-eluting stents), suggest that shorter durations (3 to 6 months) of DAPT may be sufficient.[410,411] Current guidelines recommend delaying elective non-cardiac surgery until completion of the full course of DAPT and, whenever possible, performing surgery without discontinuation of aspirin.[312]

Regarding BMS, several studies confirm that the first month following BMS placement is a high-risk period for non-cardiac surgery. However, most guidelines on stent type, surgical timing for both DES and BMS and antiplatelet cessation should probably be re-evaluated, as other underlying factors may explain postoperative MACE in these patients. In a large national, retrospective cohort study of 41 989 operations occurring in the 24 months after a coronary stent implantation between 2000 and 2010, a nested case–control study assessed the association between perioperative antiplatelet cessation and MACE.[412] Within 24 months, 28 029 patients underwent non-cardiac operations resulting in 4.7% MACE. After adjustment, the three factors most strongly associated with MACE were non-elective surgical admission, history of myocardial infarction in the 6 months preceding surgery, and revised cardiac risk index more than 2. Of the 12 variables in the model, timing of surgery ranked fifth in explanatory importance measured by partial effects analysis, and stent type ranked last.

10.3. Anticoagulant agents

10.3.1. Heparin

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 to 3 h. **1A**

We suggest that severe bleeding associated with SC 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 the dose guided by aPTT. **2C**

We suggest that severe bleeding related to SC LMWH should be treated with intravenous protamine at a dose of 1 mg per 100 antifactor Xa units of LMWH administered and, if unresponsive, with a further 0.5 mg protamine per 100 antifactor Xa units. **2C**

10.3.2. Fondaparinux

Recommendation

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

Although some research is ongoing,[413] currently there is no available drug acting as an antidote to fondaparinux. rFVIIa has been proposed to control severe bleeding, but limited data support this.[414]

10.3.3. Vitamin K antagonists

Recommendations

We recommend that VKAs should not be interrupted in patients undergoing low bleeding risk procedures: skin surgery, dental and oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomies), nor for most ophthalmologic surgery [i.e. mainly anterior chamber (cataract)]. **1C**

We recommend that for low–moderate thrombotic risk patients (e.g. atrial fibrillation patients with $CHADS_2$ score ≤ 4; patients treated for >3 months for a non-recurrent VTE) undergoing procedures requiring INR less than 1.5, VKA should be stopped 3 to 5 days before surgery (acenocoumarol, warfarin). 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 thrombotic risk patients (e.g. atrial fibrillation patients with a $CHADS_2$ score >4; patients with recurrent VTE treated for <3 months or patients with a prosthetic cardiac valve); warfarin: last dose 5 days before surgery; 4 days before surgery, no heparin; 3, 2 and 1 day before surgery, LMWH (last dose 24 h before surgery) or SC UFH twice or thrice daily; day 0, surgery; acenocoumarol: 3 days before surgery, last dose; 2 and 1 day before surgery, same protocol as for warfarin. **1C**

We suggest that the therapeutic dose of LMWH or UFH should be tailored for each patient, depending on the respective thrombotic and bleeding risk. **2C**

We recommend that for low bleeding risk patients, VKAs should be restarted during the evening or the day after the procedure (at least 6 h after). Therapeutic doses of LMWH should be given postoperatively until the target INR is observed in two following measurements. **1C**

We recommend that for moderate to high thrombotic risk patients, prophylactic doses of heparin (UFH or LMWH) should be started during the evening or the day after the procedure (at least 6 h after) and given for up to 48 to 72 h, and then therapeutic anticoagulation should be resumed. VKA can restart at that time or later, only when surgical haemostasis is achieved. **1C**

In VKA-treated patients undergoing an emergency procedure, we recommend that INR must be measured on the patient's admission to the hospital, with the administration of four-factor PCC to reverse VKA anticoagulant effects (e.g. at an initial dose of 25 IU factor IX kg^{-1} at an INR of 4) rather than the transfusion of plasma. **1B**

In bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the administration of four-factor PCC 25 to 50 IU factor IX kg^{-1} plus 5 to 10 mg IV vitamin K. **1B**

If PCC is not available, then in bleeding patients where VKA-induced coagulopathy is considered a contributing factor, we recommend the transfusion of plasma (15 to 20 ml kg^{-1} plus 5 to 10 mg IV vitamin K. **1C**

Preoperative interruption of VKA therapy with substitution by a short-acting anticoagulant such as LMWH or UFH (so-called bridging therapy) is common practice. However, recent studies have indicated that it may increase perioperative bleeding without decreasing thrombotic events.[415–417] Nevertheless, practice guidelines which have not taken these more recent studies[415–417] into account support bridging therapy when there is a high thrombotic risk, especially in mechanical valve patients.[418]

For urgent control of the anticoagulant effects of VKA, the administration of PCC provides faster and more effective reversal than FFP.[419–422] The optimal dosing of PCC has not been fully elucidated, so the dose should be individualised to maximise effectiveness without compromising safety. Overcorrection should be avoided as this may increase thrombotic risk. Dose selection may be influenced by the patient's clinical status, pretreatment INR, target INR and other laboratory values.

10.3.4. Direct oral anticoagulants

Recommendations

We recommend assessment of creatinine clearance in patients receiving DOACs who are scheduled for surgery. **1B**

We suggest that DOACs should only be withheld the day before surgery for patients undergoing low bleeding risk procedures such as skin surgery, dental and oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but no polypectomies) and most ophthalmologic surgery. **2C**

For intermediate and high bleeding risk procedures:

(1) *we recommend that rivaroxaban, apixaban and edoxaban should not be given for 2 days before the procedure (i.e. last oral intake 3 days before), pending a creatinine clearance (Cockcroft–Gault formula) above 30 ml min^{-1}. No bridging therapy is needed.* **1C**
(2) *we recommend that dabigatran should not be given for 3 days before the procedure (i.e. last oral intake 4 days before), if the creatinine clearance is above 50 ml min^{-1} and 4 days before the procedure (i.e. last oral intake 5 days before), if the creatinine clearance is between 30 and 50 ml min^{-1}. No bridging therapy is needed.* **1C**

We suggest that in severe bleeding patients treated with dabigatran, a specific antidote (idarucizumab) should be considered. **2C**

We suggest that for low bleeding risk procedures, when haemostasis is achieved, DOACs should be recommenced during the evening after the procedure (at least 6 h after). **2C**

We suggest that for intermediate and high bleeding risk procedures, prophylactic doses of LMWH or DOACs (according to specific indications) should be given postoperatively whenever VTE prophylaxis is requested and then the full therapeutic dose of DOAC should be resumed up to 72 h postoperatively, when surgical haemostasis is achieved. **2C**

10.3.4.1. Rivaroxaban

Rivaroxaban is an orally active oxazolidone derivative and the first available oral antifactor Xa agent.

In the EINSTEIN_PE study, rivaroxaban was as effective as enoxaparin plus adjusted-dose VKA, but the major bleeding rate was halved in the rivaroxaban group.[423] Rivaroxaban has also been studied in patients hospitalised for acute medical issues and/or infection with elevated risk factors for VTE (MAGELLAN study).[424] In these patients, a 10-mg dose of rivaroxaban once daily for 35 days was compared with a once-daily prophylactic dose of enoxaparin (40 mg) for only 10 days. The efficacy of rivaroxaban was non-inferior to that of enoxaparin, but the frequency of bleeding was significantly higher in the rivaroxaban group (4.1 versus 1.7%; $P < 0.0001$).

The ATLAS-TIMI 51 trial was a randomised, double-blind study in patients with ACS.[425] Patients received the antiplatelet therapy chosen by their cardiologist in addition to rivaroxaban (2.5 or 5 mg twice daily) or placebo. The efficacy endpoint was incidence of cardiovascular death, myocardial infarction or ischaemic stroke. Compared with placebo, patients receiving either dose of rivaroxaban had a reduced frequency of these events. Moreover, the lower dose of rivaroxaban (2.5 mg twice daily) was also associated with a reduction in cardiovascular mortality and all-cause mortality. Treatment with the twice-daily 2.5 mg dose resulted in fewer fatal bleeding events than the twice-daily 5 mg dose (0.1 versus 0.4%; $P = 0.04$).

10.3.4.2. Apixaban

Apixaban is an oral, reversible, direct factor Xa inhibitor related to rivaroxaban. AMPLIFY was a randomised, double-blind study that compared apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (SC enoxaparin, followed by warfarin) in 5395 patients with VTE.[426] The primary efficacy outcome (recurrent symptomatic VTE or death related to VTE) occurred in 59/2609 patients (2.3%) in the apixaban group compared with 71/2635 (2.7%) in the conventional-therapy group (relative risk, RR, 0.84). Major bleeding was reported in 0.6% of patients receiving apixaban and in 1.8% of those receiving conventional therapy (RR, 0.31; $P < 0.001$ for superiority). The composite outcome of major bleeding and clinically relevant non-major bleeding occurred in 4.3% of patients in the apixaban group, compared with 9.7% of those in the conventional-therapy group (RR, 0.44; $P < 0.001$). In another study (ADOPT), apixaban was given at a dose of 2.5 mg twice daily for 30 days and was compared with an enoxaparin regimen of 40 mg daily for 6 to 14 days in hospitalised patients with a risk factor for thrombosis.[427] The results showed that apixaban was as effective as enoxaparin in preventing VTE; however, an increase in bleeding episodes was observed in the apixaban group. In comparison with these positive results in patients with ACS, the results of the APPRAISE-2 study, in which patients received apixaban 5 mg twice daily in combination with an antiplatelet regimen or a standard dual antiplatelet regimen, were not so encouraging.[428] Apixaban plus antiplatelet therapy was associated with an increase in major bleeding events and fatal intracranial bleedings, without any significant reduction in recurrences of coronary incidents.

10.3.4.3. Edoxaban

Edoxaban is the third oral antifactor Xa agent to be marketed. ENGAGE-AF was a randomised trial comparing two once-daily regimens of edoxaban (60 and 30 mg) with warfarin in 21 105 patients with a moderate-to-high-risk of atrial fibrillation (median follow-up, 2.8 years).[429] The primary efficacy endpoint (stroke or systemic embolism, annualised rate) was 1.5% with warfarin (median time in the therapeutic range: 68.4%), compared with 1.18% with high-dose edoxaban ($P < 0.001$ for non-inferiority) and 1.61% with low-dose edoxaban ($P = 0.005$ for non-inferiority). In the intention-to-treat analysis, there was a trend favouring high-dose edoxaban versus warfarin and an unfavourable trend with low-dose edoxaban versus warfarin. The annualised rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban ($P < 0.001$) and 1.62% with low-dose edoxaban

($P < 0.001$). The HOKUSAI-VTE study was a randomised, non-inferiority study that enrolled 8240 patients with acute VTE (4921 with deep vein thrombosis and 3319 with pulmonary embolism) who had initially received heparin.[430] Study participants received either edoxaban 60 mg once daily (30 mg once daily for patients with creatinine clearance of 30 to 50 ml min^{-1} or a body weight <60 kg) or warfarin for 3 to 12 months. Edoxaban was non-inferior to warfarin with respect to the primary efficacy outcome (recurrent symptomatic VTE), which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) ($P < 0.001$ for non-inferiority). The safety outcome (major or clinically relevant non-major bleeding) occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group ($P = 0.004$ for superiority).

10.3.4.4. Non-specific reversal agents and specific antidotes

As a first option, activated charcoal (50 g) has been shown to be very effective in healthy volunteers treated with apixaban 20 mg.[431] The mean elimination half-life for apixaban alone (13.4 h) decreased to 5 h when activated charcoal was administered at 2 or 6 h post-dose. For dabigatran, charcoal has only been tested *in vitro*. One case report is available for rivaroxaban.[432]

Treatments proposed for the reversal of the anticoagulant activity, or the control of bleeding in patients treated with DOACs include PCC and activated PCC (aPCC or FEIBA). Pre-clinical studies performed in rabbits and pigs have provided very positive data regarding the use of PCC for reversal of dabigatran and rivaroxaban[364] but not for apixaban. The efficacy of PCC has been demonstrated in healthy volunteers for rivaroxaban[433] but not for dabigatran. In some registries, PCC (and aPCC) appear to be effective for reversing the anticoagulant effects of all DOACs, although the lack of a control group limits the strength of this evidence.

Idarucizumab, the antidote which is being developed for dabigatran etexilate, is a fully humanised monoclonal antibody fragment. It completely reverses the anti-IIa activity of dabigatran. An initial series of 90 patients (either bleeding patients or patients scheduled for an invasive procedure) have been treated, and complete reversal of the anticoagulant activity was observed. However, there was a safety concern because mortality reached 20%.[434,435] Further phase 3 studies are mandatory to confirm the benefits and risks of this compound.

A factor Xa analogue (andexanet alpha), which reverses the effects of all antifactor Xa agents, is currently being developed. An injectable drug, it appears to be very effective despite having a short half-life (<90 min). This agent is not yet available in clinical practice.[436]

10.3.5. Management of patients scheduled for a procedure and treated with direct oral anticoagulants (emergency procedures excluded)

Physicians from outside the field may be unaware of the pharmacological characteristics of many DOACs. The European Society of Cardiology and several other groups, such as the Groupe d'Intérêt en Hémostase Périopératoire, have issued proposals for managing patients treated with DOACs.[437,438] The following patient groups are considered: atrial fibrillation or VTE patients treated with DOACs and undergoing an invasive procedure.

11. Comorbidities involving haemostatic derangement

11.1. Patients with comorbidities involving haemostatic derangement

11.1.1. 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 factor X deficiency causes the most frequent bleeding manifestations in amyloidosis[439] and is treated similarly to inherited factor X deficiency. Overt hypothyroidism appears to be associated with a bleeding tendency, whereas all other endocrine diseases appear to be associated with thrombotic tendency.[440]

A decrease in VWF synthesis or a decreased response to adrenergic stimulation due to hormone deficiency could be involved in the pathogenesis of hypothyroidism-associated VWS.[441] These mechanisms are supported by the reversal of VWS following hormone replacement therapy.[442] Other coagulation abnormalities described in hypothyroidism are: impaired platelet function, reduction in coagulation factors, acquired inhibitors to VWF and coagulation factors, and increased fibrinolytic activity.[441] It seems that the pattern of fibrinolytic abnormality depends on the severity of hypothyroidism, with increased fibrinolysis in overt hypothyroidism and hypofibrinolysis in subclinical hypothyroidism.[443] However, other authors have found hypofibrinolysis in both overt and subclinical hypothyroidism[444] and conclude that the association between subclinical hypothyroidism and haemostasis abnormalities requires further studies.[444] The coagulation and fibrinolysis abnormalities are corrected by hormone therapy.[445] DDAVP was also effective in patients with VWS undergoing thyroid surgery.[446]

Patients with autoimmune and malignant disorders can develop autoantibodies affecting the activity or accelerating the clearance of clotting factors (acquired inhibitors). Such inhibitors are most frequently directed against factor VIII or VWF but acquired inhibitors against other clotting factors were also described. Recommendations for the diagnosis and management of acquired inhibitors of clotting factors were recently issued.[447]

11.1.2. Patients on chronic medication associated with haemostatic derangements

It is estimated that half of the general surgical population take medication unrelated to surgery.[448] Medications other than antiplatelet and anticoagulant agents may potentially affect haemostasis, including SSRIs, antiepileptic drugs and herbal agents.

Recommendation

We suggest individualised preoperative discontinuation of SSRI treatment. **2B**

SSRIs have been associated with an increased bleeding tendency, due to serotonin depletion from platelets.[449,450] Bleeding frequency was proportionate to the degree of serotonin reuptake inhibition[451] and withdrawal of SSRI medication was recommended according to their half-life if patients were submitted to procedures with a high risk of operative bleeding.[452]

However, further studies showed variable and contradictory clinical effects of SSRIs on haemostasis, with both increases and decreases of bleeding and/or transfusion.[453–457]

Interestingly, the risk of bleeding has been reported differently for various types of surgery. In an analysis of 10 studies, intraoperative and postoperative bleeding and transfusion were higher in serotonin antidepressants (SAD) users before orthopaedic and breast surgery but not in CABG or facial surgery.[458]

Although analysis of two pharmacovigilance databases suggested that SSRIs were not associated with an increased risk of bleeding,[459] a recent systematic review including 13 relevant studies across a variety of surgical procedures showed that SADs were associated with increased risk of perioperative bleeding (odds ratio = 1.21 1.21 to 4.14) and blood transfusions (odds ratio = 0.93 to 3.71).[460] Clinicians should be aware of this increased bleeding risk with SAD use and carefully weigh it against the psychiatric benefits in all patients undergoing surgery. Discontinuation of SADs should be planned 2 weeks before the operation in patients with a high risk of bleeding and who are in a stable phase of depression. Alternatively, changing to an antidepressant that inhibits less serotonin reuptake should be considered in case of exacerbation of depression.[458] Another database analysis provides preliminary evidence that SSRIs may be associated with an increased risk of bleeding as compared with agents with lower affinity or non-selective reuptake inhibition.[461]

Moreover, when used alongside APAs, perioperative use of SSRIs should be individualised. Although a French database analysis did not demonstrate any significant association between bleeding adverse drug reactions and exposure to SSRI and APAs versus APAs alone,[462] another database analysis found a high rate of adverse reactions of SSRIs related to drug–drug interactions.[463] Some SSRIs may interfere with warfarin metabolism and increase INR.[464]

In both large population-based cohort studies,[465] and meta-analyses of cohort and case–control studies[466,467] SSRIs are associated with an increased risk of UGIB. The risk is higher even after short-term use, especially in male patients.[468] Combination with NSAIDs[466,467] and antiplatelet drugs[467] significantly increases the risk of UGIB. The use of acid-suppressing drugs significantly reduces the risk.[467]

Recommendation

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

Drug interactions may involve antiepileptic drugs and warfarin.[464] Most commonly used antiepileptic drugs are either potent hepatic enzyme inducers or inhibitors and they affect the metabolism of warfarin. The antiepileptic drug valproic acid may displace warfarin from the protein binding sites resulting in significant INR changes, but this type of drug interaction is less well known.[469]

The effect of valproic acid on haemostasis is controversial. Decreased platelet function and numbers, as well as reduced levels of factors VII, VIII, XIII, VWF, fibrinogen, protein C and antithrombin were described in some studies.[470–472] However, in one prospective controlled study, there were no statistically significant differences in any of the studied haemostasis parameters in cases versus controls.[473] Any clinically relevant detriment to haemostasis is uncommon.[474]

Recommendation

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

Although herbal remedies are used to treat a large variety of diseases, the safety of many products has not been proven, nor has their effect on blood parameters been determined. As a number of herbal preparations have been reported to cause alteration of haemostasis, some authors recommend their discontinuation before undergoing any surgical procedure.[475] Moreover, some Chinese herbal medicines (such as danshen, dong quai, ginger, ginkgo, liquorice and turmeric) demonstrate

pharmacodynamic interactions with conventional anticoagulant/antiplatelet drugs resulting in increased bleeding risk.[476]

A recent narrative review provides an exhaustive list of the potential effects on haemostasis of different herbal medicines.[477] Many of them reduce platelet aggregation *in vitro*. In addition, some interact with antiplatelet and anticoagulant drugs.

Ginkgo biloba is one of the most widely used herbal medicines in Europe. Although *in vitro* studies show inhibition of platelet aggregation, clinical trials currently do not support its use as an antiplatelet drug. Although case reports of spontaneous bleeding after taking ginkgo preparations have been reported,[478] a randomised placebo controlled, double-blind study in healthy volunteers found no effect of an extract of ginkgo biloba on bleeding time and coagulation.[479] A meta-analysis of 18 RCTs did not indicate a higher bleeding risk associated with standardised ginkgo biloba extracts provided as daily oral therapy.[480] Neither the combination of ginkgo biloba with aspirin,[481,482] cilostazol[483] nor ticlopidine[484] affects coagulation indices.

Diet and nutrients may also alter platelet function and preoperative testing of platelet function may be required.[485] Omega 3 polyunsaturated fatty acids reduce fibrin generation measured by overall coagulation potential in healthy subjects.[486] The clinical perioperative significance of these *in vitro* studies is unknown.

11.2. Patients with congenital bleeding disorders

11.2.1. Preoperative assessment

Recommendations

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

We recommend the use of BATs for detecting and predicting the perioperative risk of bleeding before surgery and invasive procedures. **1C**

IBDs can be classified as primary or secondary haemostatic defects, which include VWD, platelet disorders and coagulation factor deficiencies, respectively. It is estimated that at least 1% of the population have an IBD.[487] However, there are probably many more individuals with undiagnosed IBDs. They can be detected preoperatively by using BATs, which include a structured patient interview and an interpretation grid to score for the most severe presentation of each bleeding symptom resulting in an individual bleeding score.[488]

Prospective studies found that structured bleeding questionnaires have a high negative predictive value but a low/moderate positive predictive value both in adults[488–491] and in children referred for diagnosis.[492,493] A bleeding score more than 3 could generally be considered as suggestive of a bleeding diathesis in adults[494] but age and gender differences have been reported.[495] The validity of the bleeding score has never been proven in patients having a severe bleeding disorder.

In patients with a suspected IBD, further testing should be carried out by the haematologist as the efficacy of laboratory testing in patients with mucocutaneous bleeding is low.[496] It is also of paramount importance to distinguish between trivial bleeding symptoms, which are frequently reported by normal subjects, and clinically relevant bleeding symptoms that should be more carefully considered.[497] The discriminative power of a bleeding score to differentiate significant from trivial bleeding has been recently assessed in healthy children.[498] When children with a total bleeding score of at least 3 were predicted to have VWD, the sensitivity, specificity, positive predictive value and negative predictive value were 97.2, 97.1, 48.6 and 99.9%, respectively, making the bleeding score a reliable tool for evaluating children with suspected VWD.

In a prospective observational cohort study including 796 patients with different types of VWD, a bleeding score more than 10 could predict bleeding events that were severe enough to require treatment.[499] Similar results were also observed in patients with type 2 VWD, where those patients with a bleeding score more than 9 showed a nearly 6-fold higher risk of bleeding than those with a bleeding score in a normal range.[500]

11.2.2. General perioperative management

Recommendations

Surgery can be safely performed in patients with IBDs when there is appropriate careful preoperative planning, appropriate replacement/substitution therapy, and multidisciplinary team management. **C**

We recommend that patients with IBDs be managed perioperatively in collaboration with a haematologist, preferably in dedicated centres with expertise in coagulation disorders. **1C**

We suggest preoperative haemostatic correction in patients with IBDs depending on the type of surgery. **2C**

Once considered an absolute contraindication, surgery in patients with IBDs is still challenging due to the risk of haemorrhagic complications. However, recent data demonstrated that good surgical results are achievable over a range of procedures when there is appropriate careful preoperative planning, appropriate replacement/substitution therapy, and multidisciplinary team management.[501–506] Although surgery is a highly demanding intervention in patients with severe IBDs, especially in low-resource countries,[507] it often represents a life or limb-saving and quality of life-improving measure, which has to be taken.

In one survey performed in 26 comprehensive haemophilia centres in Europe, the mean rate of haemorrhagic complications in major surgery was 10%.[508] Despite higher perioperative bleeding complications in patients with IBDs,[509] postoperative outcomes similar to matched pairs without IBDs was also reported.[504,510–513]

During recent decades, total knee replacement has been the most common surgical intervention performed in adult patients with haemophilia. The medium and long-term results of primary TKA in 74 patients with haemophilia showed good prosthetic survival at 5 and 10 years, with an excellent relief of pain.[514] However, an analysis of a US database for postoperative complications up to 8 years after TKA in patients with haemophilia ($n = 3396$) and VWD ($n = 1379$), compared with a matched cohort of patients without bleeding disorders ($n = 427\,132$ and $n = 384\,657$, respectively), found significantly higher rates of infection, transfusion of blood products, medical complications and revision after TKA in patients with IBDs.[515]

Outcomes in general and abdominal surgery,[516,517] pseudo-tumour[518,519] and cancer surgery,[520] urological interventions,[511] laparoscopic surgery,[504] cardiac interventions,[521–523] and colonoscopies[524] have also been reported. Different types of surgery are performed successfully in patients with inhibitors, too.[525–527] However, delivery outcome in women with IBDs is unsatisfactory, given the high PPH incidence despite specialised care.[528]

Further evidence of the safety and efficacy of surgical procedures comes from reviews of surgical outcomes in children with IBDs.[529–531] The most frequent interventions are circumcision, dental procedures, insertion of central venous access devices and tonsillectomy.

In the largest national cohort, including 508 tonsillectomy in patients with either VWD or haemophilia, the immediate haemorrhage rate was 1.6%, similar to the rate in the general healthy population. However, delayed haemorrhage occurred in 15%, substantially higher than the 1 to 3% reported in healthy patients.[530] Small case series studies in children with IBDs undergoing adenotonsillar procedures report variable rates of haemorrhage: lower,[532–535] similar,[536,537] or higher[538] than in healthy patients. These data suggest that perioperative protocols could be improved to reduce bleeding risk further.

Circumcision is frequently performed in children with IBDs, with variable outcomes.[529,539] The rate of bleeding complications in haemophilia patients varies from low (0–6%)[512,540–542] to high incidence[543] depending on the centre and protocol used. However, when the IBD is not diagnosed before intervention, the bleeding rate can be even higher.[541] The importance of sufficient replacement therapy and peri-procedural collaboration with a haematologist is supported by the result of a large retrospective study performed in Iran.[544] Among 423 cases with various IBDs, the global bleeding rate after circumcision was 57%, in contrast with no bleeding complications in 151 patients correctly managed.

Low rates of bleeding were also reported in dental extraction in patients with IBDs.[545–548] However, there are concerns about the best pathway of treatment, and guidelines for the provision of dental treatment in patients with IBDs were recently issued.[549,550] Although patients with mild IBDs can be allowed' the majority of routine non-surgical dental treatment is in a community-based dental practice and successful management involves close collaboration between dental services and haemophilia centres.[551]

Surgery in patients with IBDs should be performed under the supervision of, or in consultation with, a haematologist specialised in coagulation disorders, preferably in dedicated centres with appropriate facilities for investigation and treatment.[506,508,552–558] A multidisciplinary team approach and individualised preoperative management plan with surgery performed in haemophilia treatment centres is highly recommended to minimise the risks.[525,559,560] The methodology of certification of these centres in Europe has been recently published.[561]

There is insufficient evidence from RCTs to assess the most effective and well tolerated treatment to prevent bleeding in patients with IBDs[562]; however, major and minor surgeries are performed in these patients following national and international recommendations based on data from observational, uncontrolled studies.

The mainstay of perioperative therapy in patients with IBDs is to provide the deficient factor both at the time of invasive procedures and afterwards: 1 to 5 days for minor surgery and 7 to 14 days for major surgery.[508,557,559] The specific requirements of such patients in the perioperative period will be discussed below in the setting of the underlying condition.

11.2.3. Specific perioperative management

11.2.3.1. Von Willebrand disease

Recommendations

We recommend DDAVP as a first-line treatment for minor bleeding/surgery in patients with VWD, after a trial testing. The standard regimen is 0.3 $\mu g\,kg^{-1}$ dissolved in 50 ml saline and infused IV over 20 to 30 min, repeated every 12 to 24 h usually for no more than 3 days. **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**

VWD is the most common hereditary bleeding disorder with an estimated prevalence of 0.6 to 1.3%.[557] Bleeding

in VWD is due to impaired platelet adhesion and/or reduced levels of factor VIII. Acquired VWS comprises defects in VWF concentration, structure or function arising from medical disorders or treatments.

Reviews and guidelines covering the management of VWD have been published.[563,564] These state that patients should be managed in specialised centres where experienced haematology and laboratory support is available. 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 DDAVP; replace VWF using plasma-derived concentrates; and promote haemostasis with antifibrinolytic drugs or platelet transfusion.

Despite a lack of RCTs investigating DDAVP in VWD, DDAVP has been shown to increase plasma VWF and factor VIII from two-fold to more than five-fold over baseline levels, with good or excellent results in most surgical adult patients[565–567] as well as children.[533,537,568,569] Although the use of DDAVP during pregnancy is controversial,[570] efficacy has been reported in obstetrical bleeding in women with bleeding disorders.[571]

A literature and current practice survey performed by the European Haemophilia Therapy Strategy Board confirms that DDAVP can be used effectively to cover minor surgery and dental procedures in most VWD patients.[572] The standard DDAVP dose is 0.3 $\mu g\,kg^{-1}$ dissolved in 50 ml saline and infused intravenously over 20 to 30 min, repeated every 12 to 24 h,[557] usually for no more than 3 days unless the patient is monitored closely, and switched to factor concentrate if tachyphylaxis occurs.[572] The peak response is registered at 1 h and the plasma concentrations of factor VIII and/or VWF should be checked again at 4 h to identify patients in whom clearance is increased.[572] As not all VWD patients are responsive to DDAVP, a test infusion is recommended. A positive response to DDAVP is defined as increases of factors VIII : C and VWF : RCo to more than 0.3 to 0.5 IU dl^{-1}.[570,572] Response rates are reduced in children less than 2 years old.[568]

Tachyphylaxis[570] and hyponatraemia[573] are frequent but not sustained adverse effects of DDAVP.

VWF can be supplied by cryoprecipitate or human plasma-derived concentrates. A phase 3 trial of recombinant VWF has been recently published.[574]

Currently licensed plasma-derived VWF concentrates in all countries are virally inactivated formulations with varying ratios of VWF to factor VIII ranging from approximately 1 : 1 to 2.4 : 1.[575] Products with a VWF/factor VIII ratio more than 1 are preferred in the management of VWD.[576] However, prevention of bleeding during surgery, especially in emergency situations where higher levels of coagulant factors are needed promptly, is better achieved with products that have a higher concentration of factor VIII.[557] A combination of high purity factor VIII and high purity VWF concentrate could be also used in emergencies.[563]

Plasma-derived VWF concentrates may prevent excessive bleeding in more than 90% of VWD patients.[576] The efficacy has been confirmed in surgical paediatric[577–581] and adult patients with VWD.[566,577,580,582–594] However, type 3 and type 2 VWD variants may be extremely difficult to manage and there is no guarantee that homeostasis will be achieved even when plasma concentrations have apparently been corrected into the normal range.[563]

For bleeding treatment/prevention in major surgery, a loading dose of 40 to 60 U kg^{-1} is recommended, with 20 to 40 U kg^{-1} every 8 to 24 h for maintenance for 7 to 14 days.[557] For minor surgeries, the doses are slightly lower, given less frequently and for a shorter duration (1 to 5 days). However, the regimen should be individualised as the dosing of a concentrate is dependent on the patient's own basal VWF level, the pharmacokinetics of a specific product, and the nature and severity of the bleeding or the procedure.[579,580,595,596]

Perioperative monitoring of factor VIII : C and VWF : RCo may help determine appropriate dosing.[557] For severe bleeding or prophylaxis for major surgery, VWF : RCo and factor VIII levels should be 100 to 200 IU dl^{-1} and 100 to 250 IU dl^{-1}, respectively.[557] Subsequent dosing should maintain VWF : RCo and factor VIII levels above 50 IU dl^{-1} for 7 to 10 days.[557,563,580] For prophylaxis for minor surgery, VWF : RCo and factor VIII levels should be more than 30 IU dl^{-1} (preferably >50 IU dl^{-1}) maintained for 1 to 5 days.[557] Bleeding time and PFA-100 time are not reliable methods for perioperative monitoring[563] and their use is controversial.[597]

Adverse reactions to VWF concentrates include allergic and anaphylactic reactions.[577] VWF concentrates contain factor VIII, so carry a potential thromboembolic risk.[598,599] Maintaining levels less than 250% for factor VIII : C and less than 200% for VWF : RCo may reduce thrombogenicity.[557] Antithrombotic prophylaxis should be considered when other risk factors exist, particularly during periods when VWF and factor VIII levels are in the normal or supranormal range.[600]

Antifibrinolytic therapy may facilitate effective clotting. Outcomes with regimens using EACA in addition to DDAVP in adenotonsillar surgery have been variable.[537,538] For adults, a dose of 4 to 5 g EACA (oral or intravenous) is recommended, followed by 1 g h^{-1} until bleeding is controlled, or for 5 to 7 days postoperatively. Tranexamic acid is given intravenously at a dose of 10 mg kg^{-1} every 8 to 12 h.[557,601]

11.2.4. Platelet defects

Recommendations

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

We suggest that 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**

Although rare, the prevalence of inherited platelet disorders (IPDs) is probably underestimated due to underdiagnosis.[602] IPDs are heterogeneous in severity, mechanisms and frequency and few are characterised at the molecular level. IPDs can alter platelet production, morphology and function and many classification schemes have been proposed.[555,603]

Prominent IPDs include Glanzmann thrombasthenia (defective platelet integrin alpha IIb β_3 receptor) and Bernard–Soulier syndrome (dysfunction or absence of receptor GPIb/IX/V). Both conditions may cause severe bleeding.[555,604] Bleeding with other platelet abnormalities is usually mild/moderate, so they are described as mild bleeding disorders (MBDs);[555] VWD is included in this category. Typically they are manifested as mucocutaneous bleeding, or bleeding following trauma, or invasive surgical or dental procedures.

Diagnosis of platelet defects is challenging as they may be undetectable via bleeding history.[555] No relationship is apparent between bleeding severity and VWF/platelet function variables and in one study the diagnostic efficacy of laboratory testing for hereditary mucocutaneous bleeding was only 40%.[496] PFA-100 has a high rate of false positive and false negative results and does not predict bleeding risk.[555,605] PFA-100 clotting times are not sufficiently sensitive to be recommended as a haemostasis screening test,[606] although they correlate with the severity-of-bleeding history.[607] Recently, international recommendations on the laboratory diagnosis of IPDs were issued.[608]

Guidelines on the management of patients with IPDs, including for during the perioperative period, were also published.[555,609] The therapies include DDAVP, rFVIIa, platelet transfusions and antifibrinolytics.

In a review of DDAVP use in IPDs' efficacy appears variable in both mild and severe platelet defects.[603] Most evidence supporting the clinical efficacy of DDAVP in IPDs comes from case reports or small case series,[555] and one old placebo-controlled study.[610] The latter found that DDAVP shortened bleeding time and was sufficient for perioperative management in selected patients, particularly in those with normal dense platelet granule stores. In a prospective study of 5649 unselected patients for elective surgery, 254 patients were diagnosed with either acquired or inherited impaired primary haemostasis using a PFA-100 device. Preoperative treatment of these 254 patients with DDAVP led to normalisation of platelet dysfunction in 90% of cases and there was no statistically significant difference in blood transfusion compared with the patients without impaired haemostasis.[611] Further case series support the efficacy of DDAVP in perioperative bleeding prophylaxis management in some mild IPDs.[612]

The DDAVP-induced improvement of primary haemostasis in patients with aspirin-like defect is mainly due to the marked increase of the VWF.[613] However, the quantitative laboratory measurement of the response to DDAVP in patients with IBDs other than VWD or haemophilia is still uncertain, and the use of DDAVP remains empirical.[570] Recently, it was shown that DDAVP selectively enhances the platelet procoagulant activity which appears to be an additional mechanism to the increase of VWF level.[614]

Efficacy has rarely been shown in Glanzmann thrombasthenia.[604] If DDAVP is contraindicated or is not effective, patients should receive platelet transfusion or rFVIIa.[555]

A recent review of the literature identified one registry, one open-label study and 40 case reports, including a total of 172 bleeding episodes and 62 procedures, in patients with Glanzmann thrombasthenia treated with rFVIIa.[615] Reported efficacy in perioperative bleeding management was more than 90%. However, this may not be solely due to rFVIIa but due to combined multi-modal therapy. There were five thromboembolic events registered.

An international post-marketing registry of rVIIa usage included 96 patients with Glanzmann thrombasthenia treated for 216 surgical procedures (minor 179, major 37) between 2007 and 2011.[616] In total, 49 patients had antibodies/refractoriness to platelet transfusion. For all patients, regardless of platelet antibody or refractoriness status, rFVIIa administered with or without platelets and/or antifibrinolytics provided effective haemostasis with a low frequency of adverse effects. In patients without antibodies/refractoriness, rFVIIa showed 100% effectiveness for both minor and major procedures, similar to that for platelet transfusion. In patients with platelet antibodies/refractoriness, the effectiveness of rFVIIa was 91% and 100% for minor and major procedures respectively, comparable to that for platelets. rFVIIa was also effective in the treatment of non-surgical bleeding in patients with Glanzmann thrombasthenia.[617]

No reliable data exist concerning rFVIIa in bleeding due to platelet dysfunction, and the drug is not licensed for other IPDs.

In the registries mentioned above, platelet transfusion was also effective in the treatment of both surgical and non-surgical bleeding in patients with Glanzmann thrombasthenia.[616,617] The effectiveness of platelets in patients with antibodies or refractoriness may be due to the transient nature of the inhibitors.

Eltrombopag, an oral agonist of the thrombopoietin receptor, has been used successfully instead of platelet transfusion for raising the platelet count in patients with MYH9-related disease.[618]

The use of antifibrinolytic drugs in IPDs is not evidence-based. They stabilise the clot and are useful as adjunctive therapy.[555,604] However, tranexamic acid was shown to partially reverse effects of clopidogrel in cardiac surgery.[619] This effect may contribute to the effectiveness of antifibrinolytics alone in surgical and non-surgical bleeding in patients with IPDs, such as Glanzmann thrombasthenia.[616,617] 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.[620]

11.2.5. Haemophilia A and B

Recommendations

We recommend adequate perioperative replacement therapy to ensure well tolerated 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 DDAVP as first-line perioperative therapy in patients with mild haemophilia A as long as factor VIII can be raised to an appropriate therapeutic level. **2C**

Haemophilia is a recessive X-chromosome-linked IBD, characterised by deficiency of coagulation factor VIII (haemophilia A) or factor IX (haemophilia B). These deficiencies are due to mutations of the respective clotting factor genes, and affect male offspring of the carrier females.[559] The estimated frequency is 1 : 10 000 births, with haemophilia A representing 80 to 85% of the total haemophilia population.

Haemophilia patients may develop spontaneous bleeding into joints and/or bleed excessively after injury or surgery.[559] The clinical severity of the bleeding correlates with the degree of deficiency. The severity of haemophilia is currently classified according to the plasma levels of factors VIII or IX activity: severe if less than 1%, moderate if between 1 and 5% and mild if between 5 and 40% of normal.[621] Mildly affected patients bleed excessively only after trauma or surgery and may have normal routine coagulation test results.[622] Some carrier females have reduced coagulation factor levels and this is important when specific replacement therapy may be required.[559]

Factor replacement therapy can induce antifactor VIII or antifactor IX antibodies, known as 'inhibitors'. These are more common in severe forms of haemophilia.[556] Development of inhibitors in mild haemophilia can change the bleeding phenotype from mild to severe.[622]

Acquired haemophilia is a rare but potentially life-threatening haemorrhagic disorder caused by the development of auto-antibodies against factors VIII or IX. It may be associated with malignancy, autoimmune disorders, drug reactions, or pregnancy.[623]

Factor assays are necessary to determine the diagnosis and monitor the therapy.[559] Global assays have the potential to offer a more objective measure of both the haemophilic phenotype and the response to treatment, in particular in patients who develop inhibitors to deficient clotting factors and who require bypassing agents (e.g. FEIBA) for haemostasis.[624]

Haemophilia therapy involves infusion of deficient coagulation factors, either prophylactically or during bleeding. Mild haemophilia may be treated with DDAVP and tranexamic acid rather than coagulation factors.[556]

Although high-quality studies are lacking, in a literature review and survey of European practice, replacement therapy appeared efficacious in the perioperative management of haemophilia A.[508] In most settings there was agreement on the intensity and duration of replacement therapy between published data and clinical practice. The lack of consensus on the optimal replacement therapy is more evident for children and the types of procedures that may be performed in this age group.[529] Furthermore, in the youngest children the half-lives of factors VIII and IX are shorter and more frequent dosing is required.[529]

The clinical effects of different coagulation factor levels have not been investigated, and the minimum required haemostatic levels for individual factors cannot be

defined.[625] Consequently, the World Federation of Hemophilia (WFH) guidelines recommend different regimens for factor replacement depending on the availability of resources.[559] Conversely, a high-level clotting factor replacement regimen which maintains the preoperative high level for a longer period appeared to favour wound healing and to decrease the infection rate in TKA.[626]

In rare situations where monitoring factor VIII activity is not possible in patients with haemophilia undergoing elective or emergency orthopaedic surgery, the feasibility and safety of a standardised regimen (50 to 70 IU kg^{-1} preoperatively, followed by 30 to 40 IU kg^{-1} every 8 to 12 h for 1 to 3 days, 20 to 30 IU kg^{-1} every 8 to 12 h for days 4 to 10 and then every 24 h until end of intensive rehabilitation) has been reported.[506]

FFP and cryoprecipitate have relatively low levels of clotting factors and also have the potential for viral transmission. These products are indicated only if concentrates are not available.[559]

Although both plasma-derived and recombinant factor VIII products proved efficacious for preventing/treating bleeding episodes in haemophilia patients, the preference for one or another product has been highly debated.[627,628] The WFH recommendations do not express a preference for either recombinant or plasma-derived products,[559] and a 4-year surveillance study did not detect a class or brand differences in inhibitor development.[629] The safety and efficacy of recombinant factor VIII have been shown in further observational studies in patients undergoing surgery.[630,631]

Moreover, a prospective cohort study showed that the degree of factor VIII purity, but not the source of the product, influences inhibitor development independently from other risk factors.[632] A recent meta-analysis showed that high-intensity treatment is a strong risk factor for inhibitor development; the effect of the type of factor VIII was largely due to confounding.[633]

In haemophilia B, there is also evidence that both plasma-derived and recombinant products are effective in perioperative management,[591,634–639] providing similar outcomes to those observed among non-haemophiliacs.[640]

Continuous infusion of replacement factors may reduce 'wasteful' peaks followed by sub-therapeutic low concentrations, when compared with bolus infusion.[641] For severe haemophilia A patients undergoing surgery, continuous infusion has been shown to reduce factor VIII 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.[642–645] Increased risk of inhibitor development has been linked with continuous infusion,[646] but other data do not confirm this risk.[630,647]

Continuous infusion is used in nearly half of patients undergoing major orthopaedic surgery.[508] A non-interventional study in 12 centres, including 12 patients with severe haemophilia A having 28 surgeries, indicated that 95% of factor VIII measurements were on target, with efficacy and tolerability rated as good/excellent.[648] Short-term central catheters can be used perioperatively for continuous infusion.[649]

Continuous infusion of factor IX has also been associated with excellent haemostasis and safety.[502,639]

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 factor VIII, or non-activated) or rFVIIa.[650–653]

Retrospective[654] and prospective[655] studies have confirmed the efficacy of aPCC, with criteria for satisfactory haemostasis met in over 80% of cases. Very few serious adverse events were reported in these series.

For PCC, recent consensus publications recommend 75 to 100 IU kg^{-1} given preoperatively, and then at 8 h intervals for 7 days and following this, at 12 h intervals for up to three weeks.[503,656] Despite concerns about potential thrombogenic risks, concomitant use of tranexamic acid is increasingly used.[657]

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 0.025% for the procedures included in that analysis.[658] Further post-marketing surveillance,[659] analysis of databases, [653,660,661] and literature reviews[662] found similar results in patients undergoing surgery.

The safety of higher than licensed doses of rFVIIa has been recently supported by other studies.[663] Children have a faster clearance of rFVIIa and higher doses are also advocated.[529]

Adjunctive tranexamic acid was found to be safe, well tolerated and effective in patients with haemophilia and inhibitors[664] and is highly recommended, provided there are no contraindications.[659]

The relative effectiveness of rFVIIa and aPCC for the treatment of acute bleeding in haemophilia patients with inhibitors was investigated by Cochrane reviews.[650,665] Similar haemostatic effects for rFVIIa and aPCC were reported, without increasing thromboembolic risk. In contrast, a Bayesian meta-regression indicated rFVIIa as being more effective in the treatment of joint bleeds in patients with inhibitors.[666] However, the UK guidelines recommend both bypass agents at recommended licensed doses and, if the original therapy fails, the use of the alternative agent.[667] Further studies document that both rFVIIa and aPCC can be used successfully perioperatively.[525,668,669]

In the absence of comparative studies carried out in the surgical setting, then personal experience, availability and cost may guide the choice of the bypassing agents.[670] The choice of product in patients with high-titre inhibitors is highly individualised, and depends on the age of the patient, prior exposure to plasma products, type of bleeding, volume of reconstitution, cost, efficacy and safety.[503] In patients who are plasma naïve or those with haemophilia B and inhibitors, rFVIIa is used to achieve rapid haemostasis. However, for patients with haemophilia A who have been previously exposed to plasma products, either aPCC or rFVIIa may be used.

The use of bypassing agents has a substantial economic impact.[671] rFVIIa appears to be cost-neutral[672] or even cost-effective[673] relative to aPCC, for mild/moderate bleeds in this patient population.

Evaluation of haemostatic response to bypassing agents using thrombin generation testing or viscoelastic tests has been proposed as a means to optimise the haemostatic management of individual patients with inhibitors for surgery.[674–676]

Potential thromboembolic risks associated with rFVIIa and aPCC have been discussed.[677,678] Currently, both rFVIIa[679] and aPCC[680,681] administration in haemophilia patients with inhibitors is considered well tolerated.

DDAVP boosts plasma levels of both VWF and factor VIII. Consequently it could be the treatment of choice for patients with mild haemophilia A when factor VIII can be raised to appropriate therapeutic levels.[559] Each patient should be tested before surgery as there are significant differences between individuals.[682] Response to DDAVP is correlated with age (higher in responders),[683,684] endogenous factor VIII:C levels,[683] and type of mutation.[683–686] Advantages over factor products include lower costs, absence of risks of transmission of viral infections and the avoidance of other potential hazards of using clotting factors. The decision to use DDAVP must be based on the baseline concentrations of factor VIII, the increment achieved and the duration of treatment required.[559] A recent review describes the few prospective and retrospective studies on the use of DDAVP in a surgical setting in patients with haemophilia A, for both minor and major procedures.[570] Another analysis of 48 patients with non-severe haemophilia A evidenced a complete or partial response to DDAVP (factor VIII:C > 0.3 IU ml^{-1}) in 77% of cases, sustained at 3 h post-administration in 50% of cases.[687] DDAVP was also haemostatically effective in 96% of bleeding events in haemophilia A patients tested as responders to DDAVP.[684] In a review of 114 adenotonsillectomy patients with mild bleeding disorders, including haemophilia, DDAVP was successfully used.[536] However, it seems that children are less responsive at a younger age.[683] These results support the use of DDAVP in short, minor surgical procedures performed on haemophilia A patients. In an otherwise normal pregnancy, DDAVP can also be used safely during delivery and in the peripartum period in haemophilia carriers.[559]

DDAVP does not affect factor IX levels and is of no value in haemophilia B.[559]

Acknowledging clot instability as a key part of the haemostatic dysfunction in haemophilia,[688] it is common practice in Europe to use antifibrinolytics as perioperative adjunct therapy.[508] Recently it was shown that tranexamic acid added to factor VIII or rFVIIa normalises clot stability, even when combined with the lowest dose of factor concentrates, supporting the concept of a more efficient, reliable and cost-effective treatment of patients with haemophilia.[689]

Antifibrinolytic drugs are not recommended for treatment of patients with factor IX deficiency already receiving large doses of PCCs.[559] However, a recent report on clinical experience combining tranexamic acid and aPCC for bleeds and during surgery in patients with inhibitors, suggested that haemostasis was achieved in nearly all cases without any thromboses or disseminated intravascular coagulation.[657] When added to bypass therapy (aPCC or rFVIIa), tranexamic acid normalised clot stability in patients with haemophilia with inhibitors as compared with healthy controls without clinical or laboratory adverse effects.[688] It seems that the effect is limited to fibrin clot resistance to fibrinolysis, as tranexamic acid was found to have no effect on thrombin generation induced by aPCC.[690] In a recent literature review, concomitant therapy with anti-inhibitor coagulant complex and tranexamic acid therapy was found to be safe, well tolerated and effective in haemophilia patients with inhibitors.[664] Also, adjuvant EACA may help to control bleeding in haemophilia patients with inhibitors.[691] Interestingly, EACA was also effective in cases where aPCC was either not available or had been ineffective.[691]

The antifibrinolytics alone are particularly indicated in dental care, where the high fibrinolytic activity of saliva may more easily destabilise the relatively weak clot.[691] WFH recommends that EACA or tranexamic acid be started before replacement therapy.[559] The dose of EACA, which should be started the night before or in the morning of the procedure, is 50 to 100 mg kg^{-1} every 4 to 6 h for 5 to 10 days (maximum 24 g per 24 h). The dose for tranexamic acid is 25 to 50 mg kg^{-1} orally every 6 to 8 h for 10 days. A liquid preparation of these drugs may be used as a mouthwash.[559]

Tranexamic acid, without prophylactic factor replacement or DDAVP pre-procedure, was also effective in preventing bleeding following standard endoscopic procedures (without biopsy) in patients with IBDs, including mild and severe haemophilia.[692]

Antifibrinolytics for 7 days and DDAVP given before circumcision and the day after is a suitable approach in patients responsive to DDAVP.[529] Fibrin glue and/or antifibrinolytics seem to be routine practice for most centres performing circumcision.[529]

When perioperative factor substitution is adequate, the risk of venous thrombosis might be considered.[693] An analysis of pooled data from a published series of haemophilia patients undergoing arthroplasty showed an estimated incidence of symptomatic VTE of 0.5%.[694]

Although routine pharmacological thromboprophylaxis is controversial in haemophiliac patients undergoing major orthopaedic surgery, half of the comprehensive haemophilia centres in Europe reported using pharmacological antithrombotic prophylaxis after major orthopaedic surgery,[508] in contrast to 37% of respondents to a US survey[695] and 4% in a retrospective analysis of one US centre.[696] However, one centre reported that 82% of haemophiliacs received perioperative VTE prophylaxis after the year 2000 with no evidence of increased bleeding complications.[517] Individualised antithrombotic therapy, based on local clinical experience, guidelines for non-haemophilia patients and the patient's clinical characteristics is recommended.[697]

11.2.6. Rare bleeding disorders

Recommendations

There is insufficient data to recommend routine perioperative supplementation of deficient factors in patients with RBDs.

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

If rFVIIa is given to control perioperative bleeding in inherited factor VII deficiency, we suggest lower doses (e.g. 20 to 25 $\mu g\,kg^{-1}$ every 4 to 6 h) than in haemophilia patients with inhibitors. **2C**

There is insufficient data to recommend rFVIIa in perioperative bleeding for patients with other RBDs.

There is insufficient data to recommend peri-procedural DDAVP or antifibrinolytic drugs in patients with mild RBDs.

RBDs include inherited deficiencies of coagulation factors other than factors VIII and IX, for example deficiencies of fibrinogen, prothrombin, factor V, factor VII, factor X, factor XI, factor XIII, various combined factor disorders, as well as vitamin K-dependent clotting factor deficiencies which include factor II, factor VII, factor IX and factor X.[556,698] The prevalence of RBDs is low, between 1 : 500 000 and 1 : 2 000 000,[699,700] accounting for 3 to 5% of inherited coagulation disorders.[701] Factor VII and XI deficiencies are the most common RBDs.[698]

Clinical manifestations of the different RBDs are heterogeneous and include mucocutaneous, joint and organ bleeds. The utility of standard coagulation screening tests is limited by the test's sensitivity at very low residual factor levels.[698] Tests evaluating global haemostatic capacity can assess more effectively the rate or total thrombin generated, whole blood clot formation, and/or fibrin polymerisation. Thrombin generation tests[702,703] and thromboelastography[704] may provide accurate evaluation of *in vivo* haemostasis and treatment response and be better suited to predict clinical phenotype, particularly in factor XI deficiency where standard assays fail to correlate with bleeding risk.[698]

The best treatment options, doses and management approaches for patients with RBDs published in different guidelines and reviews are based on descriptive studies and expert opinion with low levels of evidence.[556,698,699,704–706] The treatment mainstay for RBDs is replacement of the deficient coagulation factor and use of adjunctive therapies (antifibrinolytics, oestrogen/progestogen) where appropriate. Unfortunately, as regards RBDs, compared with haemophilia, the safety and efficacy data for the few available products are limited, as is experience in their optimal use.

Coagulation factor supplementation is generally advisable for less than 0.5 to 1 g l^{-1} fibrinogen[699] and less than 20 to 30% for other coagulation factors.[698] For specific factor deficiencies, plasma-derived concentrates are available for fibrinogen, factor VII, factor XI, and factor XIII but also, recombinant factors are available for factor VII and factor XIII. rFVIIa is the treatment of choice for factor VII deficiency. If rFVIIa is not available, plasma-derived factor VII is favoured over PCC because of PCC's potential thrombogenicity.[556] PCCs are recommended for factor II or factor X deficiencies. However, evidence supporting prophylactic use of PCCs in factor II[707,708] or factor X deficiency is scarce.[709,710] For factor XI deficiency, both factor XI concentrate and virally inactivated FFP are reasonable, although tranexamic acid alone may suffice for minor procedures.[556]

Bleeding risk in RBD patients is largely assessed by referring to case reports and expert opinion.[699–701] Residual plasma levels of deficient factors do not always predict the bleeding tendency. A European registry, based on data from 489 patients, documented that the minimum level to ensure complete absence of clinical symptoms is different for each disorder.[711] There is a strong association between residual coagulant activity and clinical bleeding severity for deficiencies of fibrinogen, factor X, factor XIII and combined factor V + factor VIII.[712] There is a weak association between residual coagulant activity and clinical bleeding severity for isolated factor V and factor VII deficiencies.[712] Residual factor XI activity did not predict clinical bleeding severity.[712] For example, among factor XI-deficient women giving birth, 70% experienced no PPH, suggesting no relationship between factor XI levels and the risk of

PPH.[713] Similarly, no difference in PPH was seen in deliveries with or without prophylaxis in women with factor VII deficiency.[714] Perioperative bleeding in patients with RBDs is treated by supplementing the deficient factor.[706] However, the minimum required levels of coagulation factors levels have not been defined. The choice to use haemostatic regimens before surgery and the type of regimen is made according to the availability of products, levels of deficient factor, type of surgery and anaesthesia, the tissue/organ involved, and the severity of the personal and family history of bleeding.[715,716] For example, risk of bleeding after surgery in patients with factor XI deficiency is particularly high if anatomical sites rich in fibrinolytic activity are involved.[713,716] Although deficiency in factor XI is not correlated with a haemorrhagic phenotype, a correct diagnosis and appropriate management can dramatically decrease the bleeding rate during surgery or peripartum.[716]

Surgical and peri-procedural experience in patients with specific RBDs is scarce, and the bleeding complication rates are variable.[716–728] In some cases, surgery was uneventful without supplementation of the deficient factor.[715,721]

rFVIIa is the treatment of choice for factor VII deficiency.[706] The recommended dose of rFVIIa for factor VII deficiency is 20 to 25 $\mu g\,kg^{-1}$ every 4 to 6 h, individualised according to bleeding phenotype[698] and supplemented until wound healing is established.[706] However, a wide rFVIIa dose range, dosing intervals and treatment durations have been reported in factor VII deficiency.[729,730] Continuous infusion of rFVIIa has also been reported as well tolerated, effective and highly cost-effective in factor VII deficiency.[731,732]

In a prospective international web-based registry (STER, Seven Treatment Evaluation Registry) which includes 41 surgical operations performed in 34 subjects with documented congenital factor VII deficiency, haemostatic efficacy was observed in 88% of major surgical procedures safeguarded with rFVIIa.[722] Bleeding occurred in three cases in which rFVIIa was given at low doses. The effective regimen was calculated as at least 13 $\mu g\,kg^{-1}$ per single dose with at least three doses per day, and the first dose given on the day of surgery. In the 29 minor surgical procedures, haemostatic efficacy with rFVIIa was 100%.[723] The mean daily doses ranged from 4.8 $\mu g\,kg^{-1}$ to 300 $\mu g\,kg^{-1}$. Factor VII antibody was observed in one patient undergoing a multiple dental extraction. No thromboses were reported. The same group published two further studies confirming the efficacy of rFVIIa in spontaneous or traumatic bleeds in factor VII deficiency patients.[724,726] A regimen of rFVIIa (90 to 100 $\mu g\,kg^{-1}$ weekly), split into three divided doses, proved to be both efficacious and well tolerated in the long-term prophylaxis of bleeding in severe deficiency of factor VII.[726]

Registry data suggest that rFVIIa treatment may control or prevent bleeding in other RBDs, with a favourable safety profile.[733] Low-dose rFVIIa (33 to 47 $\mu g\,kg^{-1}$) also appears to be well tolerated and effective for surgery in patients with severe factor XI deficiency and inhibitors.[734] Co-administration of tranexamic acid has also proved effective,[735,736] although it may increase thrombotic risks. Elsewhere, effective haemostasis was reported in 100% of factor XI deficient patients receiving prophylactic rFVIIa before dental procedures, and minor or major surgery.[678] 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 factor XI, but that rFVIIa may not be suitable for patients with pre-existing thrombotic risk factors.

However, these data are insufficient to make a recommendation for using rFVIIa in other RBDs apart from factor VII deficiency.

DDAVP has also been used in RBDs, especially in mild cases. Limited data suggest a potential role for DDAVP in the treatment of bleeding episodes or prevention of postoperative bleeding in mild factor XI defects.[716,737]

Antifibrinolytic agents may be given to patients with RBDs, particularly for mucosal bleeding or bleeding prevention following dental extractions.[556,706,723,732]

Thrombosis is a major concern with coagulation factor supplementation. Afibrinogenaemia, factor VII or factor XI deficiencies may be associated with venous or arterial thrombosis, spontaneously or after deficient factor supplementation.[699–701,711,717,720,733,738–740] Inherited or acquired thrombotic risk factors may coexist with the underlying defect. However, there are no data on patients with RBDs pertaining to the use of prophylaxis to prevent postoperative VTE, particularly after orthopaedic surgery. Therefore, replacement therapy must be individualised and associated antithrombotic prophylaxis in mild factor deficiencies must be considered.[741]

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