



JOHN WILEY & SONS, LTD, THE ATRIUM, SOUTHERN GATE, CHICHESTER P019 8SQ, UK

*****PROOF OF YOUR ARTICLE ATTACHED, PLEASE READ CAREFULLY*****

PLEASE AIM TO RETURN YOUR CORRECTIONS WITHIN 48 HOURS OF RECEIPT OF YOUR PROOF, THIS WILL ENSURE THAT THERE ARE NO UNNECESSARY DELAYS IN THE PUBLICATION OF YOUR ARTICLE

☐ **READ PROOFS CAREFULLY**

ONCE PUBLISHED ONLINE IT IS NOT POSSIBLE TO MAKE ANY FURTHER CORRECTIONS TO YOUR ARTICLE

- This will be your only chance to correct your proof
- Please note that the volume and page numbers shown on the proofs are for position only

☐ **ANSWER ALL QUERIES ON PROOFS** (Queries are attached as the first page before the proof.)

- List all corrections and send back via e-mail to the production contact as detailed in the covering e-mail, or mark all corrections directly on the proofs and send the scanned copy via e-mail. Please do not send corrections by fax or post

☐ **CHECK FIGURES AND TABLES CAREFULLY**

- Check size, numbering, and orientation of figures
- All images in the PDF are downsampled (reduced to lower resolution and file size) to facilitate Internet delivery.
- Review figure legends to ensure that they are complete
- Check all tables. Review layout, title, and footnotes

☐ **COMPLETE LICENSE AGREEMENT if you have not already signed one**

- Please login into Author Services; where via the Wiley Author Licensing Service (WALS) you will be able to complete the license agreement on behalf of all authors. **Your article cannot be published unless we have received the signed license agreement.**

☐ **OFFPRINTS**

- Free access to the final PDF offprint or your article will be available via Author Services only. Please therefore sign up for Author Services if you would like to access your article PDF offprint and enjoy the many other benefits the service offers.

Additional reprint and journal issue purchases




- Should you wish to purchase additional copies of your article, please click on the link and follow the instructions provided: www.sheridan.com/wiley/eoc
- Corresponding authors are invited to inform their co-authors of the reprint options available.
- Please note that regardless of the form in which they are acquired, reprints should not be resold, nor further disseminated in electronic form, nor deployed in part or in whole in any marketing, promotional or educational contexts without authorization from Wiley. Permissions requests should be directed to mailto: permissionsuk@wiley.com
- For information about 'Pay-Per-View and Article Select' click on the following link: <http://olabout.wiley.com/WileyCDA/Section/id-404512.html>

AUTHOR QUERY FORM

Dear Author,

During the preparation of your manuscript for publication, the questions listed below have arisen. Please attend to these matters and return this form with your proof.

Many thanks for your assistance.

Query References	Query	Remarks
Q1	Please check if link to ORCID is correct.	
Q2	Please confirm that given names (blue) and surnames/family names (vermilion) have been identified and spelled correctly	
Q3	Please provide volume number and page range for ref. 74 if available at proof stage	

Strategies to minimize intraoperative blood loss during major surgery

A. Shah^{1,3}, A. J. R. Palmer² and A. A. Klein⁴

¹Radcliffe Department of Medicine and ²Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, and ³Nuffield Department of Anaesthetics, Oxford University Hospitals NHS Foundation Trust, Oxford, and ⁴Department of Anaesthesia and Intensive Care, Royal Papworth Hospital, Cambridge, UK

Correspondence to: Dr A. Shah, Radcliffe Department of Medicine, University of Oxford, Level 4 Academic Block, John Radcliffe Hospital, Oxford OX3 9DU, UK (e-mail: akshay.shah@linacre.ox.ac.uk)

Background: Reducing operative blood loss improves patient outcomes and reduces healthcare costs. The aim of this article was to review the current surgical, anaesthetic and haemostatic intraoperative blood conservation strategies.

Methods: This narrative review was based on a literature search of relevant databases up to 31 July 2019 for publications relevant to reducing blood loss in the surgical patient.

Results: Interventions can begin early in preoperative phase through identification of patients at high risk of bleeding. Directly acting anticoagulants can be stopped 48 h before most surgery in the presence of normal renal function. Aspirin can be continued for most procedures. Intraoperative cell salvage is recommended when anticipated blood loss is greater than 500 ml and this can be continued after surgery in certain situations. Tranexamic acid is safe, cheap and effective, and routine administration is recommended when anticipated blood loss is high. However, the optimal dose, timing and route of administration remain unclear. The use of topical agents, tourniquet and drains remains at the discretion of the surgeon. Anaesthetic techniques include correct patient positioning, avoidance of hypothermia and regional anaesthesia. Permissive hypotension may be beneficial in selected patients. Promising haemostatic strategies include use of pharmacological agents such as desmopressin, prothrombin complex concentrate and fibrinogen concentrate, and use of viscoelastic haemostatic assays.

Conclusion: Reducing perioperative blood requires a multimodal and multidisciplinary approach. Although high-quality evidence exists in certain areas, the overall evidence base for reducing intraoperative blood loss remains limited.

Paper accepted 12 September 2019

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.11393

Introduction

Approximately 313 million surgical procedures are done worldwide each year¹. Recent estimates show that at least 4.2 million people die within 30 days of surgery each year, which accounts for 7.7 per cent of all deaths globally². Estimates of postoperative complications and morbidity are even higher^{3,4}. Perioperative bleeding remains a major risk during and after surgery, and is associated with a high rate of death, complications and healthcare resource use^{5–8}.

The mechanisms contributing to non-vascular, non-traumatic intraoperative bleeding are complex, and include pre-existing co-morbidity, type of surgical procedure, activation of fibrinolytic and inflammatory pathways^{9–11}, and acquired haemostatic impairment

secondary to haemodilution, consumption¹², medications (such as anticoagulants and antiplatelets), hypothermia and acidosis¹³.

Advances in anaesthesia, surgery and transfusion medicine over the past decade have led to the development of 'patient blood management', a multimodal, evidence-based strategy consisting of three pillars: treating anaemia, reducing perioperative blood loss and improving tolerance to anaemia (*Fig. 1*)¹⁴. This review article discusses the organizational and intraoperative surgical, anaesthetic and haemostatic strategies that can be used to minimize blood loss and improve patient outcomes (*Table 1*). The management of major haemorrhage, perioperative anaemia and transfusion thresholds is beyond the scope of this review and is described elsewhere^{15–19}.

Fig. 1 The three-pillar, nine-field matrix of perioperative patient blood management

	First pillar: optimize erythropoiesis	Second pillar: minimize blood loss and bleeding	Third pillar: harness and optimize physiological reserve of anaemia
Preoperative	Detect, investigate and treat anaemia Treat iron deficiency Treat other haematinic deficiencies	Preoperative history Risk stratification Managing anticoagulation and antiplatelet therapies	Optimize physiological reserve and other risk factors Formulate patient-specific plans to minimize blood loss, optimize red cell mass and reduce anaemia
Intraoperative	Schedule surgery with haematological optimization	Cell salvage Anaesthetic blood conservation strategies Blood-sparing surgical techniques Meticulous surgery Pharmacological agents	Optimize cardiac output, ventilation and oxygenation Restrictive transfusion thresholds
Postoperative	Stimulate erythropoiesis Be aware of drug interactions that can increase anaemia	Vigilance for postoperative bleeding Maintain normothermia Manage anticoagulation Treat infection promptly Postoperative cell salvage	Optimize anaemia reserve Minimize oxygen consumption Avoid unnecessary phlebotomy Restrictive transfusion thresholds

Table 1 Strategies to minimize intraoperative blood loss

Organizational	Surgical	Anaesthetic	Haemostatic
Preoperative history	Tourniquet	Permissive hypotension	Desmopressin
Risk stratification	Antifibrinolytics	Neuraxial anaesthesia	Procoagulant factors
Management of antiplatelet and anticoagulant therapies	Cell salvage Drains Surgical technique Diathermy Topical agents	Patient positioning Normothermia Adequate ventilation	Viscoelastic haemostatic assays

Methods

MEDLINE, PubMed, Embase, Transfusion Evidence Library and the Cochrane Central Register of Controlled Trials were searched. The search strategy included 'surgery' in combination with the terms 'transfusion', 'blood management', 'blood conservation', 'blood loss', 'haemoglobin', 'hemoglobin'. Titles and abstracts were screened. References of all identified trials, and relevant review articles and current treatment guidelines were checked for further relevant literature. The search was restricted to literature from 1 January 2000, but older important publications were not excluded. Topics beyond the scope of this review were referenced by relevant narrative reviews, systematic reviews or clinical guidelines, where applicable.

Organizational strategies

Organizational considerations for minimizing intraoperative bleeding begin in the preoperative phase, and include

identifying patients at risk, followed by triggering pathways and initiating appropriate interventions to minimize that risk.

Preoperative history

Current UK²⁰ and European²¹ guidelines recommend taking a structured history about bleeding before surgery, which takes into account previous excessive surgical bleeding, response to haemostatic challenges, family history, and the use of antiplatelet and anticoagulant therapy. In the presence of a negative history, routine coagulation testing is not recommended as the predictive value of these tests for bleeding is poor²². For patients with a positive history of bleeding, a more quantitative description of symptoms should be obtained, along with referral to a haematologist with an interest in haemostasis for further assessment. Quantification of bleeding risk can also help in decision-making for stopping anticoagulation and planning requirements for any bridging anticoagulant

therapy that may be required. Examples of bleeding assessment tools include the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool²³, the Vicenza Bleeding Score²⁴ and the Pediatric Bleeding Questionnaire²⁵. Although none of these has been validated prospectively in a large population of general surgical patients, asking precise questions is likely to be superior to an unstructured bleeding history²⁶.

Risk stratification

Consideration should be given to the type of surgery being undertaken. Cardiac surgery, where rates of bleeding and blood product use are high, has been at the forefront of the development of surgery-specific risk scores to predict bleeding and the need for transfusion. The Papworth Bleeding Risk Score²⁷ was developed in 2010, and subsequently validated in 2015, to identify patients at risk of excessive blood loss after cardiac surgery. This score has a high negative predictive value but the positive predictive value is low: only 15 per cent of patients who were classed as high risk actually had increased postoperative bleeding²⁸. More recently, the ACTA-PORT score²⁹ has been demonstrated to be a valid, simple and accurate predictor of the risk of transfusion in patients undergoing cardiac surgery. Components of the score include: age, sex, body surface area, logistic EUROSCORE, preoperative haemoglobin and creatinine levels, and type of surgery. Such scoring systems have the potential to identify modifiable risk factors, quantify risk before surgery, allocate resources (such as cell salvage) and better guide blood service inventory management.

Managing anticoagulant and antiplatelet therapies

Increasing numbers of patients are continuing antiplatelet (for example, aspirin, clopidogrel) and anticoagulant (such as warfarin, direct oral anticoagulants (DOACs)) therapy into the perioperative phase to reduce the risk of major cardiovascular and thrombotic events. These risks must be balanced against the procedure-related risks of bleeding for an individual patient, and may require discussions with the patient, surgeon, haematologist and anaesthetist. Detailed reviews^{30–33} of the pharmacology and perioperative management of these agents can be found elsewhere, but in summary: aspirin can be continued for most procedures; bridging therapy for warfarin should be considered only in patients with the highest risk of thrombosis (for example, those with mechanical heart valves or venous thromboembolism within the previous 3 months); postoperative bridging should not be started until at least 48 h after surgery

with a high bleeding risk; DOACs, owing to their predictable pharmacokinetics, can be stopped 48 h before most operations in the presence of normal hepatic and renal function (*Fig. 2*); adenosine 5'-diphosphate receptor antagonists, such as clopidogrel, should be stopped 5–7 days before operation; and the use of tranexamic acid should be considered in patients undergoing urgent surgery with a high risk of bleeding who are on antiplatelet agents or where a residual anticoagulant effect of DOACs is suspected.

Surgical strategies

Tourniquet

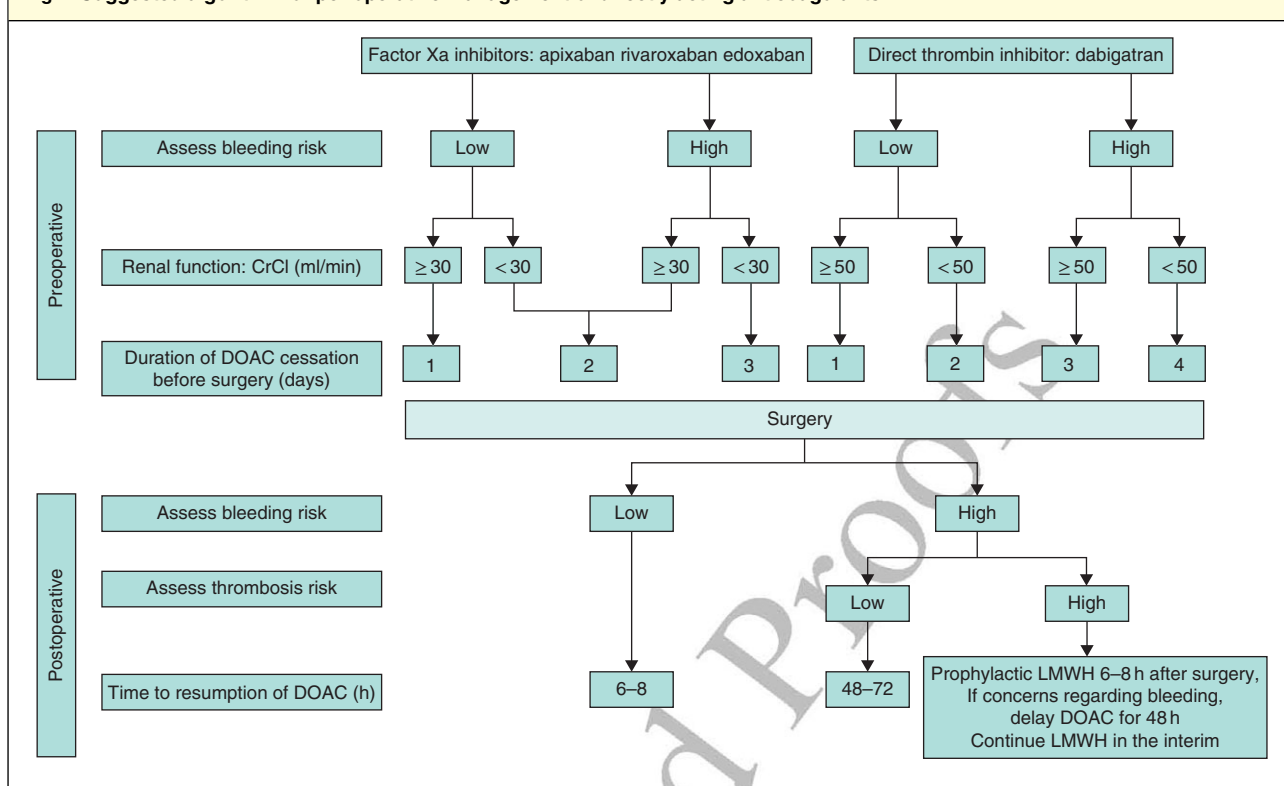
Tourniquets are used widely during limb surgery. Although they reduce intraoperative blood loss, meta-analyses^{34,35} of studies suggest that there is no difference in overall blood loss. The release of inflammatory mediators as a result of limb ischaemia may even increase blood loss³⁶. Interpretation of studies is often limited by surgeons inflating tourniquets to different pressures and for different portions of the procedure. Currently, the decision to use a tourniquet is dictated by factors other than blood management, such as visibility of the surgical field³⁷. Disadvantages of tourniquet use include increased postoperative pain, impaired quadriceps function and increased risk of thrombotic events^{34,38,39}.

Antifibrinolytics

Antifibrinolytics, such as tranexamic acid, are synthetic lysine analogues that inhibit plasminogen activation and provide clot stabilization. In the UK, tranexamic acid is recommended for all surgery where blood loss is expected to be greater than 500 ml^{40,41}. Tranexamic acid is not approved by the US Food and Drug Administration for this purpose, and epsilon-aminocaproic acid (aprotinin) may be used as an alternative. Aprotinin has been associated with increased postoperative mortality rates⁴².

A number of studies have investigated the safety and efficacy of tranexamic acid, with the majority demonstrating a reduction in blood loss and transfusion requirements. Most studies have been carried out in orthopaedic surgery, where tranexamic acid has been shown to reduce the rate of allogeneic blood transfusion by up to 69 per cent⁴³ after hip and knee surgery, without increased risk of complications, including thromboembolic events⁴⁴. Considering all surgical procedures, tranexamic acid has been shown to reduce blood loss by approximately one-third⁴⁵. It has been shown specifically to reduce blood loss, and the rate of allogeneic blood transfusions after coronary artery surgery⁴⁶,

Fig. 2 Suggested algorithm for perioperative management of directly acting anticoagulants



CrCl, creatinine clearance; DOAC, directly acting anticoagulant; LMWH, low molecular weight heparin.

spinal surgery⁴⁷, orthopaedic fracture surgery⁴⁸, prostate surgery⁴⁹, caesarean section or hysterectomy⁵⁰ and plastic surgery procedures⁵¹.

The salient area of uncertainty is the optimal route, dose and timing of tranexamic acid administration. Protocols in studies to date are extremely heterogeneous. Tranexamic acid administration can be intravenous, intra-articular, oral or in combination. Doses may be weight-adjusted and usually range from 10 to 20 mg/kg. Administration may be repeated during the intraoperative and postoperative phases⁴¹. Network meta-analyses are under way to determine an optimal dosing regimen to standardize clinical care and guide comparators for future research⁵². Potential advantages of topical delivery are that it may overcome contraindications such as renal disease owing to lower plasma levels⁵². Repeat doses to maintain therapeutic levels may play a greater role in prolonged surgery or where a large volume of blood is lost.

A further uncertainty is whether the risk of thromboembolic events has been adequately addressed in high-risk subgroups, although tranexamic acid was not associated with an increased rate of adverse events in patients undergoing major surgery for malignancy⁵³. The favourable

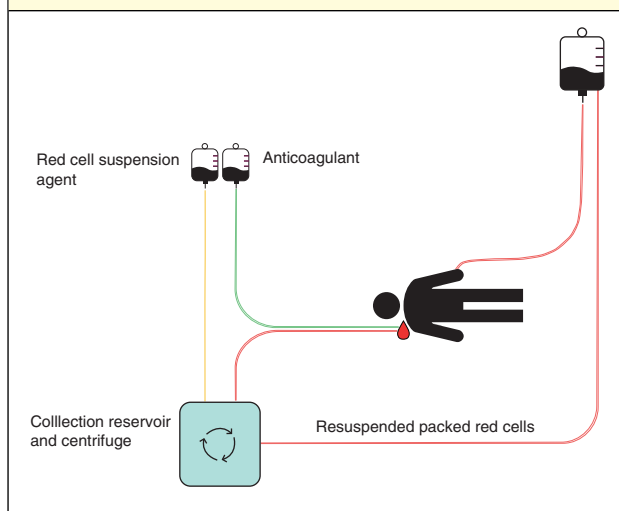
side-effect profile, cost and ready availability of tranexamic acid means that it should be considered for all surgical procedures where moderate blood loss is anticipated⁴⁰.

Cell salvage

Cell salvage is a method of recovering blood from the surgical field during the intraoperative or immediate postoperative phase that is then reinfused to the patient (Fig. 3). The National Institute for Health and Care Excellence (NICE)⁴⁰ recommends the use of cell salvage for procedures when a very high volume of blood loss is anticipated, which the recent Association of Anaesthetists guidance^{54,55} considers to be greater than 500 ml. The key principle is to use cell salvage in combination with other blood conservation strategies, when it is expected to reduce the likelihood of allogeneic blood transfusion and/or severe postoperative anaemia⁵⁵.

Intraoperative blood collection is through a suction system, whereas postoperative blood collection is through surgical drains. Collected blood is anticoagulated and filtered before reinfusion. Blood collected during surgery is typically washed and resuspended in normal saline

Fig. 3 Standard set-up of a cell salvage circuit



before reinfusion, whereas blood collected after operation through drains is typically unwashed. Current technology requires approximately 500 ml collected blood to produce a clinically valuable volume of blood for reinfusion after processing⁵⁵. Cell salvage reduces the risk of exposure to allogeneic blood by 54 per cent across all surgical specialties^{56,57}.

Procedures with significant variation in volume of blood loss make it difficult to anticipate whether sufficient blood will be collected to permit reinfusion. In this setting, cell salvage can be used in collect-only mode and processed for reinfusion only if more than 500 ml is collected. When procedures with high-volume blood loss are performed under tourniquet, postoperative rather than intraoperative cell salvage should be considered. For example, blood loss from revisional knee arthroplasty reliably exceeds 500 ml but, if performed under tourniquet, there is limited intraoperative blood loss³⁷. There remain controversies regarding which patients benefit from cell salvage, and it is not currently recommended for routine use during caesarean section^{55,58,59}.

Infection and malignancy were traditionally contraindications to cell salvage, but there is increasing evidence to support its use in these settings. With the use of a leucocyte depletion filter (40 µm), there is a 99 per cent reduction in bacterial contamination in blood resuspended in 0.9 per cent saline⁶⁰. The potentially increased risks of bacterial contamination must be weighed against the increased risk of infection through immunomodulation secondary to allogeneic blood transfusion⁶¹. Similarly, studies have not identified any association between the use of cell salvage and increased risk of metastasis during cancer surgery, and reinfused tumour cells do not have metastatic potential⁶².

When surgery requires revision of metalwork, leucocyte depletion filters do not remove small metal fragments, so selective suctioning should be employed so that the most contaminated blood is not collected⁶³.

Drains

Surgical-site drains are often used with the aim of reducing haematomas and surgical-site infection. A limited number of robust studies have investigated the effectiveness of drains in preventing postoperative complications, and many did not demonstrate any benefit of drain insertion over no drain^{64–67}. In orthopaedic surgery, conventional suction drains can increase postoperative blood loss⁶⁸.

In procedures with continuing postoperative blood loss, there may be a role for autologous reinfusion drains (cell salvage). After knee arthroplasty surgery, autologous reinfusion drains can reduce blood loss and allogeneic red blood cell transfusion rates compared with conventional suction drains or no drain^{69,70}. The value of drains is specific to each procedure. Given the increasing number of studies suggesting that drains do not confer improved clinical outcomes (and may increase blood loss), the use of drains may warrant revisiting where they are currently employed routinely.

Surgical technique

Surgical developments, including the introduction of laparoscopic and robotic surgery, are driven by a number of outcomes, but they may also reduce blood loss. In a study⁷¹ of transanal mesorectal excision for rectal cancer, operative blood loss was lower with laparoscopic than open operations, and with robotic compared with laparoscopic surgery. Similar findings have been reported in other surgical specialties^{72–75}.

Diathermy

Monopolar and bipolar radiofrequency electrosurgery are key tools for achieving haemostasis during surgery. A number of new devices are available, often in the form of bipolar sealing systems, suggested to result in less damage to adjacent healthy tissue. There is limited evidence that they reduce blood loss⁷⁶ and factors such as surgical technique are likely to be more important.

Topical agents

Topical agents including fibrin sealants (fibrinogen and thrombin), gelatine–thrombin matrices and oxidized cellulose may be applied to bleeding tissues during surgery

as a haemostatic strategy. However, these agents are expensive and, despite numerous studies across different surgical specialties, there is only weak evidence to suggest that they offer a clinically important reduction in blood loss^{77,78}.

Anaesthetic strategies

Permissive hypotension

Permissive hypotension consists of using pharmacological agents to lower intraoperative mean arterial BP to values between 50 and 65 mmHg to reduce blood flow to the surgical field. The intention is to reduce blood loss, while also improving visibility in the surgical field. This has to be balanced against the risks of organ hypoperfusion, such as delayed awakening, permanent cerebral damage, myocardial and kidney injury, and death⁷⁹. Therefore, this technique should be avoided in patients with coronary artery disease, poorly controlled hypotension or cerebrovascular disease.

Permissive hypotension can be achieved through a reduction in cardiac output, BP or a combination of these, depending on the method used. Techniques, some of which will be discussed in this review, include patient positioning, central neuraxial anaesthesia, intravenous anaesthetics (such as propofol), opioids (remifentanyl), directly acting vasodilators (nitroglycerine), selective beta-blockers (esmolol), selective α -blocker (dexmedetomidine), combined α - and beta-blocker (labetalol) and volatile anaesthetics (sevoflurane). Systematic reviews and RCTs^{80–83} have demonstrated that permissive hypotension reduces blood loss in patients undergoing orthopaedic, maxillofacial, spinal and radical prostatectomy surgery. This translated into a reduction in transfusion requirements only in orthopaedic surgery. However, all of the included studies were small, of low quality and, more importantly, did not evaluate harm. If permissive hypotension is to be undertaken, adequate patient selection is paramount and hypotension must be monitored closely to ensure adequate organ perfusion.

Central neuraxial anaesthesia

Anaesthetic techniques play an important role in minimizing intraoperative blood loss. Central neuraxial blockade (subarachnoid/epidural anaesthesia) results in blockade of preganglionic sympathetic nerve fibres, arterial hypotension and reduced peripheral venous pressures. These result in less arterial and, perhaps more noticeably, less venous oozing from the surgical site. Blockade of sympathetic nerve fibres also results in attenuation of the surgical stress

response, which in turn is associated with stabilization of clotting factors and reduced fibrinolysis^{84,85}.

Early meta-analyses^{86,87} of RCTs, conducted in a range of surgical specialties (abdominal, thoracic, pelvic, lower extremity), demonstrated that the use of neuraxial anaesthesia was associated with significant decreases in intraoperative blood loss and allogeneic red blood cell transfusion requirements. However, more recent meta-analyses^{88,89} have demonstrated no difference in blood loss or red blood cell requirements. These conflicting results should be interpreted in the context of widespread adoption of restrictive transfusion practices since much of the original research was undertaken, along with the implementation of other simultaneous blood conservation strategies as part of patient blood management.

Patient positioning

Correct patient positioning is a simple and effective intervention to reduce intraoperative blood loss. This is particularly important in patients undergoing surgery in the prone position (for example lumbar surgery). Incorrect positioning can lead to compression of the inferior vena cava with subsequent obstruction of venous return. The increase in hydrostatic pressure diverts blood towards the epidural venous plexus causing vessel engorgement and bleeding at the surgical site⁹⁰. Changes to intra-abdominal pressure may also be associated with blood loss⁹¹. In the supine position, the patient may be slightly tilted to the left to avoid inferior vena cava compression. Correct reverse Trendelenburg and lateral positions have also been demonstrated to reduce blood loss in patients undergoing endoscopic sinus surgery⁹² and hip arthroplasty⁹³ respectively. In addition, where possible, the site of surgery should be elevated above the level of the right atrium to facilitate venous drainage and reduce venous pressures.

Avoidance of hypothermia

Intraoperative hypothermia, defined as a core body temperature below 36°C, can result from many factors such as low operating theatre temperatures, evaporation from body cavities, use of cold intravenous fluids and anaesthetic gases, reduced metabolic activity, and loss of thermal regulation and responses owing to anaesthesia (such as shivering). Patients at risk of developing hypothermia include those at extremes of age, undergoing combined regional and general anaesthesia, major surgery, prolonged surgery and with higher ASA fitness grade.

The reversible adverse effects of hypothermia on platelet function and the coagulation cascade, as a result of impairment of temperature-dependent enzymatic reactions, are

well recognized^{94,95}. Even mild hypothermia has been associated with an increase in blood loss of 16 per cent, and increase in relative risk of red blood cell transfusion by 22 per cent^{96,97}. In addition, hypothermia can also lead to increased rates of wound infection⁹⁸ and cardiovascular events⁹⁹, and prolonged recovery¹⁰⁰. As a result, NICE¹⁰¹ has issued guidance on the prevention and management of hypothermia in patients undergoing surgery. Examples of strategies used to avoid intraoperative cooling include regular temperature monitoring every 30 min, ensuring that the ambient theatre temperature is at least 21°C, using active forced air warming devices and administering intravenous fluids through a fluid warmer.

Ventilation strategies

Positive pressure ventilation with minimal use of positive end-expiratory pressure (PEEP) and low tidal volumes has been advocated to reduce blood loss as it promotes venous return¹⁰². However, this is not supported by high-quality evidence and needs to be balanced against the benefits of PEEP, such as alveolar recruitment.

A recent secondary analysis, of a previously published trial¹⁰³ comparing the effect of a lung-protective strategy in patients undergoing major abdominal surgery, evaluated the effect of PEEP between 6 and 8 cmH₂O *versus* zero PEEP in patients undergoing hepatic resection surgery¹⁰⁴. The authors found that using PEEP, compared with a zero PEEP strategy, was not associated with increased bleeding.

Haemostatic strategies

Desmopressin

Desmopressin is a synthetic analogue of the naturally occurring antidiuretic hormone vasopressin. It causes a transient rise in plasma levels of factor VIII and von Willebrand factor, and has been used for the treatment of mild to moderate haemophilia A and von Willebrand disease for more than 40 years¹⁰⁵. It can be given subcutaneously or intravenously at a dose of 0.3 µg/kg. Safety considerations include the risk of developing arterial or venous thrombosis and, in rare cases, desmopressin may be associated with hyponatraemia and seizures.

Recently, its use has been expanded to other potential indications. In trauma, European guidelines¹⁰⁶ recommend administration of desmopressin to patients on antiplatelet agents. In the perioperative setting, guidelines^{107,108} suggest using desmopressin where there is demonstrable evidence of acquired platelet dysfunction secondary to drugs, uraemia or cardiopulmonary bypass.

However, the evidence for the ability of desmopressin to reduce perioperative transfusion requirements and blood loss is weak. A recent Cochrane review¹⁰⁹ of 65 trials with 3874 participants undergoing surgery found no overall benefit from desmopressin. Small reductions in blood loss and transfusion requirements were observed in patients undergoing cardiac surgery, but these were judged not to be clinically important. Many of the included trials were at high risk of bias, and the overall quality of evidence ranged from very low to moderate. Any potential benefits may be seen in specific subgroups of patients, such as those with acquired platelet dysfunction or on antiplatelet therapy¹¹⁰.

Procoagulant factors

There is growing interest in the targeted use of procoagulant haemostatic factors, mainly driven by the demonstrable lack of efficacy and safety concerns regarding fresh frozen plasma^{111,112}. These can be derived from plasma as concentrates or developed as specific recombinant factors. The potential advantages of this include more rapid availability in the emergency situation, as the current processes for thawing plasma do not apply, and better efficacy as a more concentrated source of factors is being administered. This would, in turn, lead to quicker and stronger fibrin clot formation.

Concentrates can contain multiple factors; for example, prothrombin complex concentrates contain three or four vitamin K-dependent factors at high concentrations. The main indication for prothrombin complex is in patients on anticoagulant therapy, such as warfarin, with significant bleeding or who require emergency surgery¹¹³. Conversely, single procoagulant factors are also available, most notably fibrinogen concentrate. As with desmopressin, these agents have the potential to increase the rates of thrombotic events. This has been shown clearly in clinical trials of recombinant factor VIIa in unselected patients¹¹⁴.

Fibrinogen depletion, secondary to haemodilution and/or consumption, is thought to occur before deficiencies of other coagulation factors become apparent during haemorrhage¹¹⁵. Hypofibrinogenaemia is a risk factor for haemorrhage in orthopaedic surgery¹¹⁶, cardiac surgery¹¹⁷ and trauma¹¹⁵. In obstetric haemorrhage, a fibrinogen level below 2 g/l has a 100 per cent predictive value for progression from moderate to severe haemorrhage¹¹⁸. Fibrinogen concentrate is currently not licensed for acquired hypofibrinogenaemia in the UK, but is used widely in Europe. UK guidelines¹¹⁹ recommend use of cryoprecipitate as the source of fibrinogen. However, off-label use has

Table 2 Clinical practice points and research agenda for minimizing intraoperative blood loss

Clinical practice points	A multimodal strategy should be implemented to minimize intraoperative bleeding in surgical patients
	Preoperative assessment with review and management of preoperative anaemia, and antiplatelet and anticoagulant therapy
	Prophylactic tranexamic administration should be considered for all patients undergoing major cardiac and orthopaedic surgery
	Use of cell salvage and viscoelastic haemostatic assays should be considered in all cases where anticipated blood loss is > 500 ml
	Avoid hypothermia, acidosis and excessive haemodilution.
	Close collaboration between anaesthetists, surgeons and haematology is vital
Research agenda	Cost-effectiveness of viscoelastic haemostatic assays in the management of perioperative bleeding
	Safety and efficacy of haemostatic therapies such as procoagulant factors and desmopressin.
	Optimal dose, route and timing of tranexamic acid

been reported, with small studies showing reduced red cell and fresh frozen plasma transfusion requirements¹²⁰.

Despite the physiological promise of procoagulant factors, high-quality data to guide safe and effective use are lacking. A recent systematic review¹²¹ was unable to draw any conclusions owing to a paucity of data. However, the review identified 22 ongoing trials, so more definitive evidence regarding the safety, efficacy and cost-effectiveness of procoagulant factors is likely to be available in the future.

Viscoelastic haemostatic assays

Viscoelastic assays are increasingly being used in the management of severe bleeding. The two commonest assays are thromboelastography (TEG) and rotational thromboelastometry (ROTEM). The main advantage of these assays is the quick turnaround time, with an assessment of all stages of clot formation available in a few minutes. Standard laboratory tests such as prothrombin time can have a turnaround time of up to 77 min, which is not useful in a rapidly evolving situation¹²².

In brief, TEG and ROTEM measure the physical properties of clot formation in whole blood via a pin suspended in a cup heated to 37°C. The pin is connected to a torsion wire, which is connected to a transducer. The strength (or lack) of the developing clot alters the rotation of the pin, which is then converted into an electrical signal to generate a graphical output. Defects in particular parameters of clot formation allow more targeted haemostatic therapy. For example, prolonged clot initiation (R time) on TEG is suggestive of global depletion of coagulation factors and/or warfarin therapy. A detailed review¹²³ of assay machine mechanics, quality assurance and test accuracy can be found elsewhere.

Current NICE guidelines recommend the use of these assays only in patients undergoing cardiac and liver surgery, where robust cost-effectiveness data exist to support their use¹²⁴. More recent guidance from the British Society

of Haematology also suggests that TEG/ROTEM may have a role in the management of trauma and obstetric haemorrhage^{123,125,126}.

Conclusion

The potential for major intraoperative blood loss remains a key concern for surgeons and anaesthetists. Strategies to mitigate this, such as identification and management of high-risk patients, can be implemented early in the preoperative phase. During surgery, meticulous surgical techniques and local haemostasis are fundamental measures in the control of bleeding. Cell salvage is a valuable adjunct. Tranexamic acid reduces blood loss, but the optimal route, dose and timing of administration remain unclear. Additional anaesthetic techniques, such as regional anaesthesia, can also help to reduce blood loss. Other key considerations include avoidance of hypothermia, acidosis and excessive haemodilution along with early identification of coagulopathy using viscoelastic haemostatic assays. The optimal use of haemostatic therapies such as desmopressin and procoagulant factors is unclear at present, but represents an important area of ongoing research (Table 2). Close collaboration between anaesthetists, surgeons, haematologists and laboratory personnel is vital.

Acknowledgements

A.S. is currently being supported by a National Institute for Health Research Doctoral Research Fellowship (DRF-2017-10-094) and is the Trainee Fellow on the editorial board of *Anaesthesia*. A.K. is the Editor-in-Chief of *Anaesthesia*. A.A.K. or his employer has received educational grant funding, or honoraria, from, CSL Behring, Haemonetics, Pharmacosmos, Fisher and Paykel, Massimo and Vifor Pharma.

Disclosure: The authors declare no other conflict of interest.

References

- 1 Meara JG, Leather AJ, Hagander L, Aikire BC, Alonson N, Ameh EA *et al.* Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Surgery* 2015; **158**: 3–6.
- 2 Nepogodiev D, Martin J, Biccadd B, Makupe A, Bhangu A; National Institute for Health Research Global Health Research Unit on Global Surgery. Global burden of postoperative death. *Lancet* 2019; **393**: 401.
- 3 International Surgical Outcomes Study. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016; **117**: 601–609.
- 4 Biccadd BM, Madiba TE, Kluys HL, Munlemvo DM, Madzimbamuto FD, Basenero A *et al.* Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. *Lancet* 2018; **391**: 1589–1598.
- 5 Wu WC, Smith TS, Henderson WG, Eaton CB, Poses RM, Uttley G *et al.* Operative blood loss, blood transfusion, and 30-day mortality in older patients after major noncardiac surgery. *Ann Surg* 2010; **252**: 11–17.
- 6 Smilowitz NR, Oberweis BS, Nukala S, Rosenberg A, Zhao S, Xu J *et al.* Association between anemia, bleeding, and transfusion with long-term mortality following noncardiac surgery. *Am J Med* 2016; **129**: 315–323.e2.
- 7 Christensen MC, Dziewior F, Kempel A, von Heymann C. Increased chest tube drainage is independently associated with adverse outcome after cardiac surgery. *J Cardiothorac Vasc Anesth* 2012; **26**: 46–51.
- 8 Stokes ME, Ye X, Shah M, Mercaldi K, Reynolds MW, Rupnow MF *et al.* Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients. *BMC Health Serv Res* 2011; **11**: 135.
- 9 Mavrommatis AC, Theodoridis T, Orfanidou A, Roussos C, Christopoulou-Kokkinou V, Zakynthinos S. Coagulation system and platelets are fully activated in uncomplicated sepsis. *Crit Care Med* 2000; **28**: 451–457.
- 10 Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. *Anesth Analg* 2011; **113**: 1319–1333.
- 11 Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. *Br J Haematol* 2005; **129**: 307–321.
- 12 Cap A, Hunt BJ. The pathogenesis of traumatic coagulopathy. *Anaesthesia* 2015; **70**(Suppl 1): 96–101.
- 13 Martini WZ. Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. *J Trauma* 2009; **67**: 202–209.
- 14 Clevenger B, Mallett SV, Klein AA, Richards T. Patient blood management to reduce surgical risk. *Br J Surg* 2015; **102**: 1325–1337.
- 15 Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery – why, who, when and how? *Anaesthesia* 2019; **74**(Suppl 1): 49–57.
- 16 Gill R. Practical management of major blood loss. *Anaesthesia* 2015; **70**(Suppl 1): 54–57.
- 17 Curry NS, Davenport R. Transfusion strategies for major haemorrhage in trauma. *Br J Haematol* 2019; **184**: 508–523.
- 18 Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H *et al.* International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017; **72**: 233–247.
- 19 Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R *et al.* Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. *JAMA* 2019; **321**: 983–997.
- 20 Chee YL, Crawford JC, Watson HG, Greaves M. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. *Br J Haematol* 2008; **140**: 496–504.
- 21 Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G *et al.* Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2017; **34**: 332–395.
- 22 Shah A, Stanworth SJ, McKechnie S. Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia* 2015; **70**: 10–19.
- 23 Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Collier B, James P *et al.* ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost* 2010; **8**: 2063–2065.
- 24 Rodeghiero F, Castaman G, Tosetto A, Battle J, Baudo F, Cappelletti A *et al.* The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *J Thromb Haemost* 2005; **3**: 2619–2626.
- 25 Bowman M, Riddell J, Rand ML, Tosetto A, Silva M, James PD. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost* 2009; **7**: 1418–1421.
- 26 Sramek A, Eikenboom JC, Briet E, Vandenbroucke JP, Rosendaal FR. Usefulness of patient interview in bleeding disorders. *Arch Intern Med* 1995; **155**: 1409–1415.
- 27 Vuylsteke A, Pagel C, Gerrard C, Reddy B, Nashef S, Aldam P *et al.* The Papworth Bleeding Risk Score: a stratification scheme for identifying cardiac surgery patients at risk of excessive early postoperative bleeding. *Eur J Cardiothorac Surg* 2011; **39**: 924–930.
- 28 Greiff G, Pleym H, Stenseth R, Berg KS, Wahba A, Videm V. Prediction of bleeding after cardiac surgery: comparison of model performances: a prospective observational study. *J Cardiothorac Vasc Anesth* 2015; **29**: 311–319.
- 29 Klein AA, Collier T, Yeates J, Miles LF, Fletcher SN, Evans C *et al.* The ACTA PORT-score for predicting

- perioperative risk of blood transfusion for adult cardiac surgery. *Br J Anaesth* 2017; **119**: 394–401.
- 30 van Veen JJ, Makris M. Management of peri-operative anti-thrombotic therapy. *Anaesthesia* 2015; **70**(Suppl 1): 58–67.
- 31 Keeling D, Tait RC, Watson H; British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol* 2016; **175**: 602–613.
- 32 Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA *et al.* 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016; **68**: 1082–1115.
- 33 Douketis JD, Hasselblad V, Ortel TL. Bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2016; **374**: 93–94.
- 34 Zhang W, Li N, Chen S, Tan Y, Al-Aidaros M, Chen L. The effects of a tourniquet used in total knee arthroplasty: a meta-analysis. *J Orthop Surg Res* 2014; **9**: 13.
- 35 Smith TO, Hing CB. Is a tourniquet beneficial in total knee replacement surgery? A meta-analysis and systematic review. *Knee* 2010; **17**: 141–147.
- 36 Schnettler T, Papillon N, Rees H. Use of a tourniquet in total knee arthroplasty causes a paradoxical increase in total blood loss. *J Bone Joint Surg Am* 2017; **99**: 1331–1336.
- 37 Palmer A, Chen A, Matsumoto T, Murphy M, Price A. Blood management in total knee arthroplasty: state-of-the-art review. *J ISAKOS* 2018; **3**: 358–366.
- 38 Liu D, Graham D, Gillies K, Gillies RM. Effects of tourniquet use on quadriceps function and pain in total knee arthroplasty. *Knee Surg Relat Res* 2014; **26**: 207–213.
- 39 Huang Z, Xie X, Li L, Huang Q, Ma J, Shen B *et al.* Intravenous and topical tranexamic acid alone are superior to tourniquet use for primary total knee arthroplasty: a prospective, randomized controlled trial. *J Bone Joint Surg Am* 2017; **99**: 2053–2061.
- 40 Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF. Blood transfusion: summary of NICE guidance. *BMJ* 2015; **351**: h5832.
- 41 Gerstein NS, Brierley JK, Windsor J, Pannikath PV, Ram H, Gelfenbeyn *et al.* Antifibrinolytic agents in cardiac and noncardiac surgery: a comprehensive overview and update. *J Cardiothorac Vasc Anesth* 2017; **31**: 2183–2205.
- 42 Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358**: 2319–2331.
- 43 Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Oppeler M *et al.* Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014; **349**: g4829.
- 44 Franchini M, Mengoli C, Marietta M, Marano G, Vaglio S, Pupella S *et al.* Safety of intravenous tranexamic acid in patients undergoing major orthopaedic surgery: a meta-analysis of randomised controlled trials. *Blood Transfus* 2018; **16**: 36–43.
- 45 Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg* 2013; **100**: 1271–1279.
- 46 Dai Z, Chu H, Wang S, Liang Y. The effect of tranexamic acid to reduce blood loss and transfusion on off-pump coronary artery bypass surgery: a systematic review and cumulative meta-analysis. *J Clin Anesth* 2018; **44**: 23–31.
- 47 Cheriyan T, Maier SP, Bianco K, Slobodyanyuk K, Rattenni RN, Lafage V *et al.* Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. *Spine J* 2015; **15**: 752–761.
- 48 Amer KM, Rehman S, Amer K, Haydel C. Efficacy and safety of tranexamic acid in orthopaedic fracture surgery: a meta-analysis and systematic literature review. *J Orthop Trauma* 2017; **31**: 520–525.
- 49 Longo MA, Cavalheiro BT, de Oliveira Filho GR. Systematic review and meta-analyses of tranexamic acid use for bleeding reduction in prostate surgery. *J Clin Anesth* 2018; **48**: 32–38.
- 50 Topsøe MF, Settnes A, Ottesen B, Bergholt T. A systematic review and meta-analysis of the effect of prophylactic tranexamic acid treatment in major benign uterine surgery. *Int J Gynaecol Obstet* 2017; **136**: 120–127.
- 51 Murphy GR, Glass GE, Jain A. The efficacy and safety of tranexamic acid in cranio-maxillofacial and plastic surgery. *J Craniofac Surg* 2016; **27**: 374–379.
- 52 Gibbs VN, Champaneria R, Palmer A, Doree C, Estcourt LJ. Pharmacological interventions for the prevention of bleeding in people undergoing elective hip or knee surgery: a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2019; **(3)**CD013295.
- 53 Montroy J, Fergusson NA, Hutton B, Lavalley LT, Morash C, Cagiannos I *et al.* The safety and efficacy of lysine analogues in cancer patients: a systematic review and meta-analysis. *Transfus Med Rev* 2017; **31**: 141–148.
- 54 Klein AA, Arnold P, Bingham RM, Brohi K, Clark R, Collis R *et al.* AAGBI guidelines: the use of blood components and their alternatives 2016. *Anaesthesia* 2016; **71**: 829–842.
- 55 Klein AA, Bailey CR, Charlton AJ, Evans E, Guckian-Fisher M, McCrossan R *et al.* Association of anaesthetists guidelines: cell salvage for peri-operative blood conservation 2018. *Anaesthesia* 2018; **73**: 1141–1150.
- 56 Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2010; **(4)**CD001888.
- 57 Meybohm P, Choorapoikayil S, Wessels A, Herrmann E, Zacharowski K, Spahn DR. Washed cell salvage in surgical patients: a review and meta-analysis of prospective

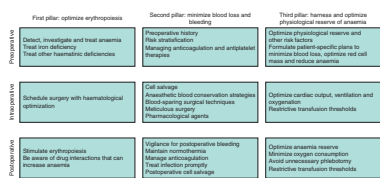
- randomized trials under PRISMA. *Medicine (Baltimore)* 2016; **95**: e4490.
- 58 Chakladar A, Fludder V, Sugavanam A. Association of Anaesthetists recommendations for cell salvage in obstetric anaesthesia. *Anaesthesia* 2018; **73**: 1575–1576.
- 59 Khan KS, Moore PAS, Wilson MJ, Hooper R, Allard S, Wrench I *et al.* Cell salvage and donor blood transfusion during cesarean section: a pragmatic, multicentre randomised controlled trial (SALVO). *PLoS Med* 2017; **14**: e1002471.
- 60 Waters JH, Tuohy MJ, Hobson DF, Procop G. Bacterial reduction by cell salvage washing and leukocyte depletion filtration. *Anesthesiology* 2003; **99**: 652–655.
- 61 Kim JL, Park JH, Han SB, Cho IY, Jang KM. Allogeneic blood transfusion is a significant risk factor for surgical-site infection following total hip and knee arthroplasty: a meta-analysis. *J Arthroplasty* 2017; **32**: 320–325.
- 62 Kumar N, Zaw AS, Kantharajanna SB, Khoo BL, Lim CT, Thiery JP. Metastatic efficiency of tumour cells can be impaired by intraoperative cell salvage process: truth or conjecture? *Transfus Med* 2017; **27**(Suppl 5): 327–334.
- 63 Morton JM, Rahn KA, Shugart RM, Wojdyla JM. Does mechanical filtration of intraoperative cell salvage effectively remove titanium debris generated during instrumented spinal surgery? An *in vitro* analysis. *Spine J* 2014; **14**: 3011–3017.
- 64 Witzigmann H, Diener MK, Kienkotter S, Rossion I, Brucker T, Werner B *et al.* No need for routine drainage after pancreatic head resection: the dual-center, randomized, controlled PANDRA trial (ISRCTN04937707). *Ann Surg* 2016; **264**: 528–537.
- 65 Denost Q, Rouanet P, Faucheron JL, Panis Y, Meunier B, Cotte E *et al.* To drain or not to drain infraperitoneal anastomosis after rectal excision for cancer: the GRECCAR 5 randomized trial. *Ann Surg* 2017; **265**: 474–480.
- 66 Khan SM, Smeulders MJ, Van der Horst CM. Wound drainage after plastic and reconstructive surgery of the breast. *Cochrane Database Syst Rev* 2015; **(10)**CD007258.
- 67 Charoenkwan K, Kietpeerakool C. Retroperitoneal drainage *versus* no drainage after pelvic lymphadenectomy for the prevention of lymphocyst formation in women with gynaecological malignancies. *Cochrane Database Syst Rev* 2017; **(6)**CD007387.
- 68 Parker MJ, Livingstone V, Clifton R, McKee A. Closed suction surgical wound drainage after orthopaedic surgery. *Cochrane Database Syst Rev* 2007; **(3)**CD001825.
- 69 Pan JK, Hong KH, Xie H, Luo MH, Guo D, Liu J. The efficacy and safety of autologous blood transfusion drainage in patients undergoing total knee arthroplasty: a meta-analysis of 16 randomized controlled trials. *BMC Musculoskelet Disord* 2016; **17**: 452.
- 70 Horstmann W, Kuipers B, Ohanis D, Slappendel R, Kollen B, Verheyen C. Autologous re-transfusion drain compared with no drain in total knee arthroplasty: a randomised controlled trial. *Blood Transfus* 2014; **12**(Suppl 1): s176–s181.
- 71 Simillis C, Lal N, Thoukididou SN, Kontovounisios C, Smith JJ, Hompes R *et al.* Open *versus* laparoscopic *versus* robotic *versus* transanal mesorectal excision for rectal cancer: a systematic review and network meta-analysis. *Ann Surg* 2019; **270**: 59–68.
- 72 Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samarutunga H, Zajdlewicz L *et al.* Robot-assisted laparoscopic prostatectomy *versus* open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet* 2016; **388**: 1057–1066.
- 73 van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA *et al.* Robot-assisted minimally invasive thoracoscopic esophagectomy *versus* open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. *Ann Surg* 2019; **269**: 621–630.
- 74 Gavriilidis P, Roberts KJ, Sutcliffe RP. Comparison of robotic vs laparoscopic vs open distal pancreatectomy. A systematic review and network meta-analysis: *HPB (Oxford)*, 2019. <https://doi.org/10.1016/j.hpb.2019.04.010> [Epub ahead of print].
- 75 Han SB, Kim HJ, Kim TK, In Y, Oh KJ, Koh IJ *et al.* Computer navigation is effective in reducing blood loss but has no effect on transfusion requirement following primary total knee arthroplasty: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 2016; **24**: 3474–3481.
- 76 Li YC, Chao A, Yang LY, Huang HY, Huang YT, Kuo HH *et al.* Electrothermal bipolar vessel sealing device (LigaSure) *versus* conventional diathermy in laparoscopic myomectomy: a propensity-matched analysis. *PLoS One* 2018; **13**: e0193611.
- 77 Polychronidis G, Huttner FJ, Contin P, Goossen K, Uhlmann L, Heidmann M *et al.* Network meta-analysis of topical haemostatic agents in thyroid surgery. *Br J Surg* 2018; **105**: 1573–1582.
- 78 Brustia R, Granger B, Scatton O. An update on topical haemostatic agents in liver surgery: systematic review and meta analysis. *J Hepatobiliary Pancreat Sci* 2016; **23**: 609–621.
- 79 Choi WS, Samman N. Risks and benefits of deliberate hypotension in anaesthesia: a systematic review. *Int J Oral Maxillofac Surg* 2008; **37**: 687–703.
- 80 Albertin A, La Colla L, Gandolfi A, Colnaghi E, Mandelli D, Giola G *et al.* Greater peripheral blood flow but less bleeding with propofol *versus* sevoflurane during spine surgery: a possible physiologic model? *Spine (Phila Pa 1976)* 2008; **33**: 2017–2022.
- 81 Boldt J, Weber A, Mailer K, Papsdorf M, Schuster P. Acute normovolaemic haemodilution *vs* controlled hypotension for reducing the use of allogeneic blood in patients undergoing radical prostatectomy. *Br J Anaesth* 1999; **82**: 170–174.
- 82 Boonmak P, Boonmak S, Laopaiboon M. Deliberate hypotension with propofol under anaesthesia for functional endoscopic sinus surgery (FESS). *Cochrane Database Syst Rev* 2016; **(10)**CD006623.

- 83 Paul JE, Ling E, Lalonde C, Thabane L. Deliberate hypotension in orthopedic surgery reduces blood loss and transfusion requirements: a meta-analysis of randomized controlled trials. *Can J Anaesth* 2007; **54**: 799–810.
- 84 Moraca RJ, Sheldon DG, Thirlby RC. The role of epidural anesthesia and analgesia in surgical practice. *Ann Surg* 2003; **238**: 663–673.
- 85 Rosenfeld BA, Beattie C, Christopherson R, Norris EJ, Frank SM, Breslow MJ *et al.* The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* 1993; **79**: 435–443.
- 86 Richman JM, Rowlingson AJ, Maine DN, Courpas GE, Weller JF, Wu CL. Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. *J Clin Anesth* 2006; **18**: 427–435.
- 87 Mauermann WJ, Shilling AM, Zuo Z. A comparison of neuraxial block *versus* general anesthesia for elective total hip replacement: a meta-analysis. *Anesth Analg* 2006; **103**: 1018–1025.
- 88 Macfarlane AJ, Prasad GA, Chan VW, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? *Clin Orthop Relat Res* 2009; **467**: 2379–2402.
- 89 Smith LM, Cozowicz C, Uda Y, Memtsoudis SG, Barrington MJ. Neuraxial and combined neuraxial/general anesthesia compared to general anesthesia for major truncal and lower limb surgery: a systematic review and meta-analysis. *Anesth Analg* 2017; **125**: 1931–1945.
- 90 Edgcombe H, Carter K, Yarrow S. Anaesthesia in the prone position. *Br J Anaesth* 2008; **100**: 165–183.
- 91 Park CK. The effect of patient positioning on intraabdominal pressure and blood loss in spinal surgery. *Anesth Analg* 2000; **91**: 552–557.
- 92 Ko MT, Chuang KC, Su CY. Multiple analyses of factors related to intraoperative blood loss and the role of reverse Trendelenburg position in endoscopic sinus surgery. *Laryngoscope* 2008; **118**: 1687–1691.
- 93 Widman J, Isacson J. Lateral position reduces blood loss in hip replacement surgery: a prospective randomized study of 74 patients. *Int Orthop* 2001; **25**: 226–227.
- 94 Reynolds L, Beckmann J, Kurz A. Perioperative complications of hypothermia. *Best Pract Res Clin Anaesthesiol* 2008; **22**: 645–657.
- 95 Buggy DJ, Crossley AW. Thermoregulation, mild perioperative hypothermia and postanaesthetic shivering. *Br J Anaesth* 2000; **84**: 615–628.
- 96 Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. *Anesthesiology* 2008; **108**: 71–77.
- 97 Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet* 1996; **347**: 289–292.
- 98 Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med* 1996; **334**: 1209–1216.
- 99 Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S *et al.* Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. *JAMA* 1997; **277**: 1127–1134.
- 100 Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI *et al.* Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology* 1997; **87**: 1318–1323.
- 101 Harper CM, Andrzejowski JC, Alexander R. NICE and warm. *Br J Anaesth* 2008; **101**: 293–295.
- 102 Bisbe E, Moltó L. Pillar 2: minimising bleeding and blood loss. *Best Pract Res Clin Anaesthesiol* 2013; **27**: 99–110.
- 103 Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A *et al.*; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013; **369**: 428–437.
- 104 Neuschwander A, Futier E, Jaber S, Pereira B, Eurin M, Marret E *et al.* The effects of intraoperative lung protective ventilation with positive end-expiratory pressure on blood loss during hepatic resection surgery: a secondary analysis of data from a published randomised control trial (IMPROVE). *Eur J Anaesthesiol* 2016; **33**: 292–298.
- 105 Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med* 2004; **351**: 683–694.
- 106 Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019; **23**: 19.
- 107 American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. *Anesthesiology* 2015; **122**: 241–275.
- 108 Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC *et al.* Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2013; **30**: 270–382.
- 109 Desborough MJ, Oakland K, Brierley C, Bennett S, Doree C, Trivella M *et al.* Desmopressin use for minimising perioperative blood transfusion. *Cochrane Database Syst Rev* 2017; (7)CD001884.
- 110 Desborough MJ, Oakland KA, Landoni G, Crivellari M, Doree C, Estcourt LJ *et al.* Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost* 2017; **15**: 263–272.
- 111 Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll D. Intensive Care Study of Coagulopathy (ISOC) Investigators. A national study of plasma use in critical care:

- clinical indications, dose and effect on prothrombin time. *Crit Care* 2011; **15**: R108.
- 112 Stanworth SJ, Grant-Casey J, Lowe D, Laffan M, New H, Murphy MF *et al.* The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children. *Transfusion* 2011; **51**: 62–70.
- 113 Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C *et al.* Guidelines on oral anticoagulation with warfarin – fourth edition. *Br J Haematol* 2011; **154**: 311–324.
- 114 Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev* 2012; (3)CD005011.
- 115 Sorensen B, Fries D. Emerging treatment strategies for trauma-induced coagulopathy. *Br J Surg* 2012; **99**(Suppl 1): 40–50.
- 116 Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Kingler A *et al.* Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. *Anesth Analg* 2007; **105**: 905–917.
- 117 Ucar HI, Oc M, Tok M, Dogan OF, Oc B, Aydin A *et al.* Preoperative fibrinogen levels as a predictor of postoperative bleeding after open heart surgery. *Heart Surg Forum* 2007; **10**: E392–E396.
- 118 Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H *et al.* The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 2007; **5**: 266–273.
- 119 Hunt BJ, Allard S, Keeling D, Norfolk D, Stanworth SJ, Pendry K; British Committee for Standards in Haematology. A practical guideline for the haematological management of major haemorrhage. *Br J Haematol* 2015; **170**: 788–803.
- 120 Morrison GA, Koch J, Royds M, McGee D, Chalmers RTA, Anderson J *et al.* Fibrinogen concentrate *vs.* fresh frozen plasma for the management of coagulopathy during thoraco-abdominal aortic aneurysm surgery: a pilot randomised controlled trial. *Anaesthesia* 2019; **74**: 180–189.
- 121 Fabes J, Brunskill SJ, Curry N, Doree C, Stanworth SJ. Pro-coagulant haemostatic factors for the prevention and treatment of bleeding in people without haemophilia. *Cochrane Database Syst Rev* 2018; (12)CD010649.
- 122 Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S *et al.* Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 2011; **39**: 2652–2658.
- 123 Curry NS, Davenport R, Pavord S, Mallett SV, Kitchen D, Klein AA *et al.* The use of viscoelastic haemostatic assays in the management of major bleeding: a British Society for Haematology guideline. *Br J Haematol* 2018; **182**: 789–806.
- 124 Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N *et al.* Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2015; **19**: 1–228, v–vi.
- 125 Collins PW, Cannings-John R, Bruynseels D, Mallaiah S, Dick J, Elton C *et al.* Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. *Br J Anaesth* 2017; **119**: 411–421.
- 126 McNamara H, Kenyon C, Smith R, Mallaiah S, Barclay P. Four years' experience of a ROTEM®-guided algorithm for treatment of coagulopathy in obstetric haemorrhage. *Anaesthesia* 2019; **74**: 984–991.

Graphical Abstract

The contents of this page will be used as part of the graphical abstract of HTML only. It will not be published as part of main article.



Reducing perioperative blood loss is a key component of patient blood management. Multimodal surgical, anaesthetic and haemostatic interventions are available, and implementation requires a multidisciplinary approach.