Blood management in total knee arthroplasty: state-of-the-art review

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ABSTRACT
Total blood loss from primary total knee arthroplasty may exceed 2 L with greater blood loss during revision procedures. Blood loss and allogeneic transfusion are strongly associated with adverse outcomes from surgery including postoperative mortality, thromboembolic events and infection. Strategies to reduce blood loss and transfusion rates improve patient outcomes and reduce healthcare costs. Interventions are employed preoperatively, intraoperatively and postoperatively. The strongest predictor for allogeneic blood transfusion is preoperative anaemia. Over 35% of patients are anaemic when scheduled for primary and revision knee arthroplasty, defined as haemoglobin <130 g/L for men and women, and the majority of cases are secondary to iron deficiency. Early identification and treatment of anaemia can reduce postoperative transfusions and complications. Anticoagulation must be carefully managed perioperatively to balance the risk of thromboembolic event versus the risk of haemorrhage. Intraoperatively, tranexamic acid reduces blood loss and is recommended for all knee arthroplasty surgery; however, the optimal route, dose or timing of administration remains uncertain. Cell salvage is a valuable adjunct to surgery with significant expected blood loss, such as revision knee arthroplasty. Autologous blood donation is not recommended in routine care, sealants may be beneficial in select cases but further evidence of benefit is required, and the use of a tourniquet remains at the discretion of the surgeon. Postoperatively, restrictive transfusion protocols should be followed with a transfusion threshold haemoglobin of 70 g/L, except in the presence of acute coronary syndrome. Recent studies report no allogeneic transfusions after primary knee arthroplasty surgery after employing blood conservation strategies. The current challenge is to select and integrate different blood conserving interventions to deliver an optimal patient pathway with a multidisciplinary approach.

INTRODUCTION
The number of primary and revision knee arthroplasty procedures continues to increase,1 and blood management strategies form a key intervention to improve outcomes and reduce costs.2 The primary goal is to reduce the severity of postoperative anaemia through preoperative optimisation and minimising intraoperative and postoperative blood loss through patient-specific approaches. Strategies to reduce blood loss may have secondary benefits to improve postoperative pain and functional outcomes.7

Total knee arthroplasty (TKA) represents major surgery that is performed on an ageing population. Over 35% of patients undergoing lower limb arthroplasty are anaemic preoperatively3 4 and over 85% are anaemic after knee arthroplasty surgery, defined by the WHO as a haemoglobin (Hb) concentration below 120 g/L for women and 130 g/L for men.6 7 The strongest risk factor for transfusion is preoperative anaemia and preoperative patient optimisation is essential.4 9

Studies report a large variation in blood loss during knee arthroplasty surgery, in part due to heterogeneous patient cohorts, surgical and anaesthetic techniques and methods of calculating the volume of blood loss.6 A study of 4769 patients who underwent primary TKA had a calculated mean total blood loss of 2181 mL (SD 931) with a mean postoperative drop in Hb concentration of 3.0 g/L (SD 1.2) and 14.6% of patients received an allogeneic blood transfusion.5 Blood loss is higher for revision procedures, although difficult to quantify due to the heterogeneity of these procedures.

This review article discusses preoperative, intraoperative and postoperative measures that can be used to deliver optimal blood management and improved patient outcomes after knee arthroplasty.

PREOPERATIVE
Preoperative anaemia
The strongest risk factor for allogeneic blood transfusion after primary and revision TKA is preoperative anaemia.4 6 The WHO defines anaemia as an Hb concentration below 120 g/L in women and 130 g/L in men. However, a recent consensus statement outlines key limitations of sex-specific thresholds when optimising patients for surgery. The same surgical procedure will result in comparable blood loss for both sexes, and therefore a higher blood loss in women relative to their circulating volume may result in higher transfusion rates.6 9 The recommended target preoperative Hb is therefore 130 g/L for both sexes.9

Preoperative anaemia is prevalent among orthopaedic patients but varies between patient population and depends on the Hb threshold used to define anaemia. Adopting a threshold of 130 g/L, Jans et al report an anaemia prevalence of 31% of patients undergoing primary TKA in Denmark,12 and the same prevalence has been reported in Spain.13 Anaemia is more prevalent in patients undergoing revision surgery in association with increasing age and comorbidities. Adopting the WHO thresholds for anaemia, the prevalence of anaemia has been
Box 1  Measuring blood loss

Research in this field is frequently limited by different measures of blood loss, making it difficult to interpret and compare studies. A key distinction is between visible and hidden blood loss. Visible blood loss is that from the operative field and in drains, whereas hidden loss includes blood lost through extravasation into tissues and residual haemarthrosis. Hidden blood loss may account for 49% of calculated total blood loss. Total blood loss is the sum of visible and hidden losses and is calculated using a number of available formulas. Many formulas require calculation of the total blood volume, typically estimated using Moore or Nadler’s formula.

Blood loss outcome measures:
- Change in haemoglobin (Hb) concentration.
- Estimated intraoperative loss.
- Drain output.
- Transfusion rate.
- Number of units transfused.
- Calculated total blood loss.

Calculated total blood loss

Many different formulas have been proposed for calculating total blood loss and those described by Gross and Mercuriali are used most frequently. Formulas to calculate total blood loss require an estimate of circulating blood volume using either the Moore or Nadler formulas.19

**Gross formula**

Estimated total blood loss (mL) = estimated blood volume × (Hct₀ − Hct₅) + mL transfused RBC, where Hct₀ is preoperative haematocrit, Hct₅ is postoperative haematocrit and Hct₅ is average of preoperative and postoperative haematocrit.

**Mercuriali formula**

Estimated total blood loss (mL of RBC) = estimated blood volume × (Hct₀ − Hct₅) + mL transfused RBC, where Hct₀ is preoperative haematocrit and Hct₅ is haematocrit postoperative day 5.

reported as 13%14 and 19%15 for primary TKA compared with 42%4 for revision TKA.

Iron-deficiency anaemia

The most frequent aetiology of preoperative anaemia is iron deficiency,9 which can be classified as absolute or functional (table 1).

<table>
<thead>
<tr>
<th>Blood results</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin &lt;30 mcg/L</td>
<td>Absolute iron deficiency</td>
</tr>
<tr>
<td>Ferritin 30-100 mcg/L and CRP &gt;5 mg/L</td>
<td>Iron deficiency in presence of inflammation</td>
</tr>
<tr>
<td>Ferritin 30-100 mcg/L and CRP ≤5 mg/L and transferrin saturation &lt;20%</td>
<td>Probable iron deficiency</td>
</tr>
<tr>
<td>Ferritin 30-100 mcg/L and CRP ≤5 mg/L and transferrin saturation ≥20%</td>
<td>Restricted iron stores for significant blood loss</td>
</tr>
<tr>
<td>Ferritin &gt;100 mcg/L and CRP ≤5 mg/L</td>
<td>Non-iron deficiency anaemia</td>
</tr>
</tbody>
</table>

Management algorithm for preoperative anaemia should be agreed locally with engagement of multidisciplinary team. CRP, C-reactive protein.

Absolute iron deficiency describes reduced or absent total body iron stores, whereas functional iron deficiency usually describes a reduced ability to mobilise iron from these stores due to chronic inflammation.9 A large number of protocols have been proposed to treat preoperative iron deficiency, which typically consist of oral iron supplementation for absolute deficiency, and intravenous iron for functional iron deficiency or where oral iron proves ineffective. Lower oral iron doses can increase efficacy and reduce gastrointestinal side effects.16 Patients diagnosed with iron deficiency anaemia must also be screened for gastrointestinal malignancy and other causes of chronic blood loss.

The diagnosis and treatment of iron deficiency anaemia increases Hb concentrations, reduces transfusion rates and improves outcomes from surgery. Evidence is limited to cohort studies, but the introduction of a preoperative anaemia algorithm reduces rates of hospital readmission and admission to critical care, length of stay, and possibly infection. Increased Hb concentrations also prevent transfusion-related complications.19 Health economic analysis reveals significant savings from preoperative anaemia screening and management.2 The benefits of treating anaemia may not purely reflect increased Hb concentrations, as iron is important for cellular processes such as oxygen transport and cellular immunity.20

Other causes of anaemia

When anaemia is not secondary to iron deficiency, alternative causes must be sought and addressed. Vitamin B₁₂ and folate deficiency account for 15% of preoperative anaemia,21 while anaemia may also result from renal, haematological and endocrine disorders. Anaemia management may therefore require input from multiple medical specialties to address the underlying cause. Besides iron supplementation, additional strategies to increase Hb concentration include administration of recombinant human erythropoietin to stimulate erthropoiesis. Erythropoietin increases preoperative and postoperative Hb in patients with TKA,22 but it is expensive and may not be approved for patient use. Erythropoietin is only recommended in specific circumstances, including anaemia secondary to chronic renal failure or when blood products are not available or acceptable to patients.23

Preoperative autologous blood donation

Preoperative autologous blood donation, where blood is donated and stored preoperatively and then administered if required postoperatively, was used widely prior to elective surgery, particularly in the USA. However, disadvantages include the potential exacerbation of preoperative anaemia and risks associated with interval reinfusion. There is also significant cost and wastage, since less than half of the preoperative blood collected is used.24 The technique is now rarely used, but may be indicated in select cases, such as patients with multiple red cell antibodies where compatible donor blood may not be available.

Optimising patients for surgery

Preoperative optimisation of anaemia requires early identification and treatment. A full (complete) blood count should be requested at the time patients are scheduled for knee arthroplasty, with renal function and group and save (type and screen). Iron studies and markers of inflammation, such as C-reactive protein, should also be included if Hb measurements are below 130 g/L in both men and women. If iron studies are normal, preoperative anaemia requires further investigation, and interventions to optimise anaemia should commence at diagnosis. Significant
increases in Hb can be obtained within 4 weeks, and there is no required minimum time between commencing iron or other therapy, and surgery. An additional scenario to consider is when patients have adequate iron stores to support erythropoiesis and are therefore not anaemic preoperatively but have low iron stores that restrict the ability to restore Hb concentration after surgical blood losses (table 1). Patients with low iron stores may therefore benefit from iron supplementation prior to surgery in the absence of anaemia, and iron studies may be appropriate for all preoperative patients.

There is no agreed Hb threshold to proceed with surgery and decisions must take into account the clinical urgency of a procedure, particularly in the case of periprosthetic fractures or infection. The lower the preoperative Hb, the higher the risk of perioperative transfusion. The goal is to correct reversible causes of anaemia prior to elective surgery, acknowledging that it may not be possible to achieve a preoperative Hb greater than 130 g/L in all patients. Correcting anaemia with perioperative transfusion is not recommended and can be detrimental to outcomes.

Preoperative management of antiplatelet agents and anticoagulants

A significant proportion of patients who undergo knee arthroplasty may take antiplatelet agents to modify cardiovascular and cerebrovascular risk, and anticoagulant agents to modify thromboembolic risk where indications include atrial fibrillation, previous thromboembolic events and prosthetic heart valves. Perioperative management of these agents is patient specific and must balance the risk of haemorrhage with the risk of thromboembolic events. Management decisions may require input from the patient, surgeon, physician and anaesthetist.

Antiplatelet agents

Antiplatelet agents inhibit platelet aggregation and thrombus formation. Most agents irreversibly bind platelet receptors, which means their action lasts the lifetime of a platelet, typically up to 10 days. It therefore takes approximately 7 days after drug cessation before platelet function is restored.

Aspirin withdrawal precedes up to 10% of acute cardiovascular events, and stopping aspirin 7 days prior to surgery in patients with high cardiovascular risk significantly increases the 30-day risk of major cardiovascular event from 1.8% to 9%. Individual studies have not identified differences in the rate of thromboembolic or bleeding events when comparing preoperative aspirin cessation or continuation. However, a meta-analysis concluded that continuing aspirin results in a 1.5 times increase in the risk of bleeding complications, but does not increase the number of bleeding complications that require medical intervention. Consensus guidelines recommend continuing aspirin monotherapy for knee arthroplasty surgery, and this strategy still allows for the use of neuroaxial anaesthesia. There is currently insufficient evidence to guide management of ADP receptor antagonist monotherapy, such as clopidogrel.

An increasing number of patients are prescribed dual antiplatelet therapy after a cardiac event or coronary revascularisation. Dual antiplatelet therapy consists of aspirin and an ADP receptor antagonist. Current guidance is to stop the ADP receptor antagonist 7 days preoperatively and to continue aspirin monotherapy.

Warfarin

Warfarin inhibits the synthesis of vitamin K dependent procoagulation factors and has a half-life of approximately 36 hours. In the acute setting, warfarin can be reversed with intravenous phytonadione or protrombin complex, and in the elective setting, warfarin must be stopped 5 days before surgery to normalise laboratory tests of coagulation. Treatment options include stopping warfarin 5 days prior to surgery with or without treatment dose bridging heparin.

Evidence to support bridging therapy with heparin is limited and studies reveal a similar risk of thromboembolic events but an increased risk of bleeding when using bridging heparin compared with no anticoagulation. Bridging anticoagulation is no longer indicated in most patients receiving warfarin for atrial fibrillation. However, it may be appropriate in patients at particularly high risk of thromboembolic events such as those who experience a venous thromboembolic event or stroke within the past 3 months, or patients with a mechanical heart valve. It is best practice to measure the international normalised ratio on the day preceding surgery to ensure there is no residual anticoagulation.

Small studies report no difference in complication or transfusion rates between individuals continuing therapeutic warfarin dose throughout surgery compared with individuals who stop warfarin and commence bridging low-molecular weight heparin (LMWH) for primary and revision knee arthroplasty. Further evidence is required before recommending this practice, which prevents the use of neuroaxial anaesthesia.

Complications after TKA are more frequent in patients taking warfarin preoperatively compared with patients not taking anticoagulants, including prolonged wound discharge, superficial and deep infection, and further surgery. However, this may reflect comorbidity rather than the anticoagulation itself.

Direct oral anticoagulants

Direct oral anticoagulants (DOAC) either inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban). They have several advantages over warfarin, including more predictable pharmacokinetics resulting in no requirement to monitor laboratory tests of coagulation. When it is desirable to monitor laboratory tests, patients require an assay of thrombin time for dabigatran and factor Xa for rivaroxaban, apixaban and edoxaban. Normal prothrombin time and activated partial thromboplastin times do not exclude residual action of DOACs. A disadvantage of DOACs over warfarin is the lack of reversal agents; however, these are under development. Idarucizumab is now available as a reversal agent for dabigatran, although this is usually only used in emergency settings.

The shorter half-life of DOACs compared with warfarin means they can be stopped closer to the date of surgery, leaving patients non-anticoagulated for a shorter period of time. In the presence of normal renal and hepatic function, guidelines recommend stopping DOACs 48 hours prior to surgery. Stopping dabigatran 48 hours prior to surgery does not result in any significant difference in perioperative bleeding events compared with stopping warfarin 5 days previously. As with warfarin, the role of bridging anticoagulation is debated and a study has shown higher rates of major bleeding and no difference in the rate of thromboembolic events when comparing no anticoagulation with bridging anticoagulation in patients with atrial fibrillation.
Retrospective studies demonstrate that unicompartmental knee arthoplasty may also be found for patient-specific knee prostheses. The same observation may reduce total blood loss during surgery by negating the need for entering the intramedullary canal; however, gains may be offset by increased operating times. The same observation may contribute to this observation. Computer navigation may increase total blood loss compared with a computer-navigated medial parapatellar approach, potentially secondary to increased operating times. Retrospective cohort studies demonstrate that increased operative time is associated with increased rates of allogeneic transfusion; however, confounding factors including the indication for surgery may contribute to this observation. Computer navigation may reduce total blood loss during surgery by negating the need for entering the intramedullary canal; however, gains may be offset by increased operating times. The same observation may also be found for patient-specific knee prostheses. Retrospective studies demonstrate that unicompartmental knee arthroplasty results in less blood loss than TKA, and that there is less blood loss with a cruciate retaining implant than a posterior stabilised implant. Implant selection may therefore affect expected blood loss from arthroplasty procedures.

**Surgical technique**

Surgical technique varies significantly between surgeons and may influence blood loss. An alternative to the traditional medial parapatellar surgical approach for TKA is the mid-vastus or subvastus approach, which can be used as part of a minimally invasive procedure. These techniques may improve early pain and range of movement, but do not reduce blood loss. A computer-navigated mid-vastus approach may even increase blood loss compared with a computer-navigated medial parapatellar approach, potentially secondary to increased operating times. Retrospective cohort studies demonstrate that increased operative time is associated with increased rates of allogeneic transfusion; however, confounding factors including the indication for surgery may contribute to this observation. Computer navigation may reduce total blood loss during surgery by negating the need for entering the intramedullary canal; however, gains may be offset by increased operating times. The same observation may also be found for patient-specific knee prostheses. Retrospective studies demonstrate that unicompartmental knee arthroplasty results in less blood loss than TKA, and that there is less blood loss with a cruciate retaining implant than a posterior stabilised implant. Implant selection may therefore affect expected blood loss from arthroplasty procedures.

**Anaesthesia**

Anaesthetic factors to reduce intraoperative blood loss include maintaining patient normothermia and reducing blood pressure. Spinal anaesthesia produces a blockade of preganglionic sympathetic nerves that reduces peripheral vascular resistance and blood pressure. During total hip arthroplasty, regional anaesthesia results in lower blood loss than general anaesthesia; however, this finding is not reliably reproduced for knee surgery, perhaps due to the use of tourniquets. The choice of anaesthetic modality should be driven by other factors such as lumbar spine pathology and recent anticoagulation.

**Box 2 Tips and tricks**

1. Obtain laboratory tests for full (complete) blood count and renal function at the time patients are scheduled for surgery.
2. Investigate the aetiology of preoperative anaemia and commence treatment at the earliest opportunity (target haemoglobin (Hb) >130 g/L for men and women).
3. Use topical, intravenous, oral or combined routes of tranexamic acid administration for all knee arthroplasty procedures.
4. Do not use conventional suction drains. Consider cell salvage for revision knee arthroplasty when significant blood loss is expected.
5. Follow postoperative restrictive transfusion regimen with Hb threshold <70 g/L except in patients with acute coronary syndrome.

**Box 3 Major pitfalls**

1. Late diagnosis or failure to address preoperative anaemia.
2. Failure to discuss blood conservation strategies with the anaesthetic team.
3. Transfusion of allogeneic blood with inappropriate clinical indication.

**Normovolaemic haemodilution** is a technique where blood is collected in the immediate preoperative period with fluid replacement to reduce the haematocrit of blood lost during surgery. Surgery is followed by autologous reinfusion of the preoperative collected blood; however, the benefits remain uncertain.22

**Tourniquet**

Tourniquet application is used by most surgeons during knee arthroplasty procedures with the goal of reducing blood loss and creating a bloodless field to improve visualisation of tissues. Proposed potential benefits also include improving cement integration with bone, which has not been supported by recent imaging studies. Patients also experience increased pain with compromised quadriceps function and a higher incidence of thrombotic events with the use of a tourniquet. Studies report conflicting outcomes with respect to the effect of tourniquet use on blood loss. Meta-analyses suggest that while a tourniquet decreases intraoperative blood loss, there is no difference in total blood loss. Tourniquet use may even increase total blood loss through the release of inflammatory mediators secondary to limb ischaemia. Surgeons may elect to have the tourniquet inflated for different portions of the procedure, and overall, the effects on blood loss do not appear to be clinically significant. The decision of whether to use a tourniquet may be guided by factors other than blood management.

**Tranexamic acid**

Tranexamic acid is a synthetic lysine analogue that competitively inhibits plasminogen activation to provide antifibrinolytic action and clot stabilisation. It is recommended for all TKA surgery in the UK, but it is not approved by the Food and Drug Administration for this purpose. Tranexamic acid has been shown to reduce the need for transfusion by 69% without increased risk of thromboembolic complications. A vast number of studies investigate the efficacy of tranexamic acid, and while they invariably demonstrate that tranexamic acid reduces blood loss and the need for transfusion, the optimal route, dose and timing of administration remain undetermined. A further uncertainty is whether the risk of thromboembolic events has been adequately addressed in high-risk subgroups. Tranexamic acid administration can be intravenous, intra-articular or oral, or in combination. Combined intra-articular and intravenous delivery has been shown to result in a greater reduction in blood loss than intravenous delivery alone for primary TKA, or intra-articular delivery alone for revision TKA. Intra-articular delivery alone may be as efficacious as intravenous or combined intra-articular and intravenous delivery for primary TKA; however, the use of different tranexamic acid doses between studies limits the interpretation. No differences in rate of thromboembolic complications have been observed with different routes of administration. There is emerging evidence that tranexamic acid reduces postoperative swelling, and improves range of movement and patient-reported outcomes after TKA. Current evidence supports the use of topical tranexamic acid with or without intravenous delivery. Oral tranexamic acid also reduces blood loss after primary TKA and requires further exploration due to lower costs. Potential advantages of intra-articular delivery are that it may overcome systemic contraindications such as renal insufficiency due to lower plasma levels. Concerns over tranexamic acid chondrotoxicity may prevent topical use in
Fibrin sealant

Topical application of fibrin sealants (fibrinogen and thrombin) to bleeding tissues is another haemostatic strategy that can be used during TKA. Meta-analyses offer contradictory conclusions as to whether fibrin sealant reduces total blood loss; however, there may be a reduction in drain output and transfusion rate without an increased risk of complications. Bipolar sealer systems do not appear to be effective as tranexamic acid at reducing blood loss and given the additional cost, the role of fibrin sealant in a multimodal blood management algorithm is uncertain.

Diathermy

Monopolar radiofrequency electrocautery is a valuable tool to achieve intraoperative haemostasis. An alternative is a bipolar sealer system that works at lower temperatures to denature collagen and seal blood vessels, which is thought to cause less damage to adjacent healthy tissues. It is challenging to quantify the effects of cautery due to variation in technique among surgeons. At present, there is insufficient evidence to recommend routine use of bipolar sealer systems to reduce blood loss, which carry a significant cost. Bipolar sealer systems do not appear to confer benefits in the presence or absence of tranexamic acid for primary TKA or in the absence of a tourniquet during revision TKA.

Cell salvage and drains

Cell salvage describes the recovery of blood from the surgical field, and it is recommended for major orthopaedic procedures where blood loss exceeds 20% of estimated blood volume. Cell salvage reduces the risk of exposure to allogeneic blood by 54% and can be performed intraoperatively by collecting blood though a suction system or postoperatively using an autologous reinfusion drain that is inserted at the time of surgery. Collected blood is anticoagulated and filtered (40 μm or leukocyte depletion filter) and can then be reinfused directly, or the red blood cells can be washed and resuspended in normal saline prior to reinfusion. Blood from intraoperative cell salvage is typically washed, whereas blood from reinfusion drains is typically unwashed, but either technique can be used in each setting. Concerns over unwashed blood include low Hb concentration, and the presence of anticoagulant and inflammatory mediators in the reinfused blood. Both washed and unwashed blood results in a hypocoagulable state, although less so with washed blood, but no difference in clinical outcomes has been identified.

Intraoperative cell salvage is less widely used than postoperative drain collection during knee arthroplasty surgery due to the frequent use of a tourniquet. In the absence of a tourniquet, cell salvage may be a valuable adjunct to blood conversation, particularly during revision surgery where there is greater blood loss. Previous contraindications to cell salvage have included bacterial infection and malignancy; however, these guidelines are now debated. When a leukocyte depletion filter is used and the collected blood is washed, there is a 99% reduction in bacterial contamination. Thus, while there is a theoretical increased risk of adverse events with reinfusion of blood with bacterial contamination, there is a definite risk of bacterial contamination from allogeneic blood transfusion. No association has been identified between the use of cell salvage and development of metastases in cancer surgery.

Conventional suction drains were widely adopted with the aim of reducing haemarthrosis and may reduce the need for dressing reinforcement, but can increase postoperative blood loss. Temporary clamping of conventional suction drains unicompartmental knee arthroplasty, but studies investigating the effect on chondrocytes are limited to in vitro experiments.

A limitation to comparing routes of delivery is that different doses and timing of delivery are used in each study, and determining the optimal regimen is a research priority. Some studies suggest reduced blood loss with higher doses of tranexamic acid (>25 mg/kg) with combined routes of administration or as a single preoperative dose. There are conflicting studies as to whether multiple doses of intravenous tranexamic acid confer a greater reduction in blood loss or allogeneic transfusion rates. Continuous intravenous infusions of tranexamic acid do not appear superior to a single bolus. Standardisation of tranexamic acid regimens would greatly aid future clinical practice in this field.

Haemostasis after TKA may be enhanced when topical tranexamic acid is supplemented with topical epinephrine. An alternative antifibrinolytic agent to tranexamic acid is α-aminocaproic acid and has demonstrated equivalent efficacy to tranexamic acid at lower cost. In the USA, the approximate cost per surgery for α-aminocaproic acid is US$2, compared with US$40 for tranexamic acid.

Box 4 Ten key publications

postoperatively only serves to reduce drain output and not total blood loss.81 Drains have not been shown to increase infection rates, despite concerns over leaving a tract into the joint, but may interfere with mobilisation after surgery, and the optimal time for drain removal has not been established.

Autologous reinfusion drains can halve the proportion of patients requiring allogeneic blood compared with conventional suction drains.82 83 However, this is not true in more recent studies with restrictive transfusion thresholds (Hb ≤80 g/L).84 In addition, autologous reinfusion drains result in a smaller reduction in allogeneic transfusion rates when compared with no conventional suction drain.83 It therefore remains unclear whether autologous reinfusion drains provide clinical benefit or cost-effectiveness when used alongside other blood conservation strategies and restrictive transfusion thresholds.84

POSTOPERATIVE

Cryotherapy

A number of compression dressings and cryotherapy strategies have been adopted to reduce blood loss; however, their role in routine clinical practice remains uncertain.85 Most studies do not demonstrate a reduction in blood loss using cryotherapy devices for knee arthroplasty.86 Assessment of new devices should take into account combined benefits in terms of blood loss, pain and functional outcomes.

Transfusion

There is a large variation in transfusion rates after TKA. A study of arthroplasty surgeons in the USA revealed transfusion rates ranging from 3.8% to 63.8% for primary TKA,87 rising to 84% for bilateral TKA.88 Studies in the UK reported transfusion rates of 2.7% for primary TKA89 and 29.1% for revision TKA.4

Transfusion rates are dictated by a number of factors, including the adoption of blood conversation strategies and different patient cohorts. Transfusion thresholds also play a role. A number of studies compared outcomes after restrictive transfusion regimens (transfusion threshold Hb 70 g/L and post-transfusion target 70–90 g/L) and liberal transfusion regimens (transfusion threshold Hb 80 g/L and post-transfusion target 80–100 g/L) for non-cardiac surgery.89 In the absence of cardiovascular disease, there is no difference between liberal regimens and restrictive in terms of functional recovery, mortality or medical complications.89 The exception is patients with ischaemic heart disease, where the risk of acute coronary syndrome may be increased with restrictive regimens.89 Recent guidelines recommend lowering the threshold for transfusion from 80 to 70 g/L in all patients except those with acute coronary syndrome.23 74 90

Restrictive transfusion regimens reduce the use of allogenic blood, and if all liberal regimens were replaced by restrictive regimens, patient exposure to blood transfusion would decrease by 43%.90 Adoption of a restrictive transfusion regimen reduces overall infection rates after orthopaedic surgery.91 In the USA, allogeneic blood transfusions after arthroplasty surgery increased over a 19-year period, although this may be secondary to reduced rates of autologous blood transfusion.92 A recent study evaluating blood conserving protocols in 376 patients undergoing primary TKA reported no autologous or allogeneic blood transfusions.88 Such low transfusion rates question whether a preparative group and save (type and screen) is required, particularly for unicompartmental knee arthroplasty where blood loss is lower than TKA.83 Given the variation in transfusion rates, such decisions should be made after local departmental audits.

Allogeneic blood transfusion carries a number of risks, including haemolytic and allergic reactions, transfusion-related acute lung injury and circulatory overload, graft-versus-host disease and transmission of bloodborne infection.93 94 Transfusion is an independent predictor of in-hospital mortality.92 There are concerns that transfusion may increase the risk of venous thromboembolism,91 and immunomodulation also increases susceptibility to postoperative infection including the lower respiratory tract, urinary tract and surgical site.95 Increased infection rates are observed with allogeneic but not autologous blood96 and leucocyte depletion decreases postoperative infection rates.97 Leucodepletion of all blood products was introduced in the UK in 1998 but is not used globally. Whether transfusion specifically increases the risk of bone and joint infection after arthroplasty surgery remains uncertain.95

Postoperative management of antiplatelet agents and anticoagulants

Patients who regularly take antiplatelet agents and anticoagulant medication prior to surgery require these postoperatively. In addition, it is recommended that physical and chemical measures are used to prevent venous thromboembolic events during the postoperative period.96 The drug, time of initiation and duration of administration, and dose of thromboprophylactic agents may influence postoperative bleeding.

When recommencing anticoagulation, the long half-life of warfarin means it can be restarted within 24 hours of surgery29 with a mean time to reach therapeutic levels in 8 days.86 Dosing warfarin can prove challenging after surgery due to the metabolic response to surgery, and an interesting development is genotype-guided dosing after hip or knee arthroplasty to reduce the risk of bleeding, venous thromboembolism and death.97 When bridging anticoagulation is indicated, the last dose of LMWH should be given 24 hours prior to the procedure and restarted 48 hours after the procedure.33 Antiplatelet agents and DOACs should be restarted once haemostasis is achieved and typically reaching full dose 48–72 hours after surgery.98

The optimal agent for chemical venous thromboprophylaxis after knee surgery is a source of great controversy, and there is significant regional variation in practice. In the UK, LWMH is most widely employed, although aspirin and prophylactic dose DOACs are recommended alternatives.98 In the USA, warfarin and aspirin are widely used. Prophylactic dose DOACs are also increasingly used for thromboprophylaxis.

The choice of agent for venous thromboprophylaxis and timing of administration may significantly influence blood loss. In the UK, thromboprophylaxis LMWH is typically commenced between 6 and 12 hours after surgery,96 whereas in the USA, it is typically commenced between 12 and 48 hours after surgery.99 In elective hip surgery, the administration of LMWH within 4 hours of surgery increased the risk of major bleeding to 6.3% compared with 2.5% when administered between 12 and 48 hours after surgery, but with a possible decrease in risk of venous thromboembolic event.99

FUTURE DEVELOPMENTS

A large number of interventions demonstrate the potential to reduce blood loss during knee arthroplasty surgery. The current challenge is to determine how to combine these interventions to deliver an optimal patient pathway. Heterogeneity of studies to date with respect to interventions and outcome measures severely limits the ability to compare the efficacy of different interventions. A consensus agreement to develop a core set of...
outcome measures and to recommend standardised treatments in future studies may facilitate progress. Collaborative trials may also overcome the small patient numbers observed in most studies published in this field, allowing adequate power to assess outcomes in patient subgroups, such as those at high cardiovascular risk. The most effective strategies to date are optimisation of anaemia, tranexamic acid delivery and restrictive transfusion strategies. It may be that further gains from additional blood conversation strategies are not clinically important or cost-effective. Nevertheless, strategies must be patient specific, and small gains may become clinically significant in select groups, such as patients with haemophilia or Jehovah’s witnesses. In addition, different algorithms will be needed for successful and cost-effective blood conservation strategies for unicompartmental knee arthroplasty, and primary and revision TKA.

CONCLUSIONS
Implementing strategies to reduce blood loss can improve patient outcomes and reduce healthcare costs. Such interventions in patients undergoing knee arthroplasty are employed preoperatively, intraoperatively and postoperatively. The strongest predictor for allogeneic blood transfusion is preoperative anaemia, and early identification and treatment reduces the rates of transfusion and complications. Intraoperatively, tranexamic acid reduces blood loss. The optimal route, dose or timing of administration remains uncertain. Postoperatively, cell salvage is a valuable adjunct for cases with significant expected blood loss. Autologous blood donation is not recommended, sealants require further evidence of benefit but may play a role in select cases, and the use of a tourniquet remains at the discretion of the surgeon. Restrictive transfusion protocols should be followed, and more current studies report no allogeneic transfusions after primary knee arthroplasty surgery.

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