Strategies to avoid intraoperative blood transfusion

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Abstract

Anaemia and blood transfusion are risk factors in the perioperative setting. Effective management begins preoperatively and should be individualized. This article addresses the current evidence base for correction of preoperative anaemia, normalization of iatrogenic and pathological coagulopathy, intraoperative strategies for optimal blood product usage and management of postoperative anaemia.

Keywords Anaemia; blood storage; blood transfusion; cell salvage

Royal College of Anaesthetists CPD Matrix: 1A02, 2A05.

Learning objectives

After reading this article, you should be able to:

- recognize preoperative anaemia and preoperative coagulopathy
- consider how to optimize the patient preoperatively in order to reduce blood loss and hence reduce the need to consider transfusion
- employ evidence-based restrictive blood transfusion appropriately in theatres and critical care
- implement intraoperative cell salvage into your theatre practice
- consider how point of care coagulation testing can assist in perioperative blood product usage

The reduction in perioperative transfusion may be achieved by implementing the three pillars of patient blood management:

- diagnosis and management of preoperative anaemia (reducing the likelihood of a haemoglobin level where transfusion needs to be considered)
- minimizing operative blood loss (optimizing surgical and anaesthetic technique, and maintaining normal coagulation)
- appropriate usage of a restrictive transfusion policy. In addition clinicians should consider the use of postoperative IV iron to accelerate recovery.[1]

During the preoperative phase it is good practice to ensure that patients are made aware of the possibility of requiring blood transfusion. They should also be informed about the alternatives that exist with respect to red cell replacement, specifically donor transfusion, cell salvage and the concept of permissive anaemia.

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Preoperative anaemia management

Anaemia in the preoperative patient is associated with worse perioperative morbidity;[2] treatment of the cause may reduce surgical risk, length of stay, perioperative transfusion and postoperative anaemia.

Investigation and treatment of anaemia is an important aspect of preparation for surgery. When iron deficiency is detected, iron replacement is indicated, and in many situations this will be best achieved using IV iron.[3] Standard preoperative investigations include

- ferritin
- iron saturation
- CRP
- eGFR
- B12
- folate.

Where appropriate, a haemoglobinopathy screen should be performed.

A low ferritin with a low iron saturation confirms iron deficiency; when the ferritin is between 30 and 100 μg/L and the iron saturation is low, the diagnosis of functional iron deficiency is more likely.[3]

Correction of coagulopathy preoperatively

Over recent years the use of anti-platelet and anticoagulant have increased. It is well established that in the acute urgent situation warfarin can be reversed with vitamin K 5 mg IV 6–8 hours prior to surgery which can restore coagulation factors. Rapid reversal can be achieved using prothrombin complex concentrate (PCC) at 25 u/kg.

Direct oral anticoagulants are more challenging; if possible, high bleeding risk surgery should be delayed for 48 hours and lower risk surgery for 24 hours, assuming normal renal function. Again if time does not permit then dabigatran can be reversed with a 5 g dose of idrucizumab. Currently there is not yet a reversal agent for direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban), although in trials of healthy volunteers andexanet are promising; currently clinical guidelines suggest the use of PCC at a larger uncapped dose of 50 u/kg (based upon in vitro research). However, trial data demonstrating improved outcomes are lacking and there are concerns regarding a potential increase in thrombotic outcome. Recent British Society of Haematology (BSH) guidelines take a pragmatic approach to proceed with surgery and consider using PCC in the event of diffuse coagulopathic bleeding.

With regard to anti-platelet agents, three randomized controlled trials demonstrating that it is safe to proceed with surgery on single agent aspirn. However, for single agent clopidogrel there is a lack of clear evidence. Regarding the use of dual anti-platelet agents there is an increased bleeding risk. Guidance is therefore to discontinue dual-antiplatelet agents 5−7 days prior to surgery.[4,5] Where this is not possible, due to the urgent need for surgery, recommendations support the use of platelet inhibition tests such as thromboelastography to assess in vivo platelet function Bleeding can be reduced by the transfusion of two pools of platelets at least 2 hours after the last dose of aspirin however the effect of larger doses of platelets for ADP antagonisists is less certain.[4,5]

Intraoperative strategies

Reduction of intraoperative blood loss requires meticulous surgical technique (which may include the application of collagen-containing products, cellulose pads or fibrin glues) and practising permissive hypotension. In addition, it is important to ensure physiological concentrations of functioning components of coagulation and inhibition of inappropriate clot lysis. The clinician must therefore ensure coagulation and platelet functions are not pharmacologically inhibited. Avoidance of hypocalaemia, hypothermia, acidosis and extreme haemodilution are important.

In trauma and penetrating injury, resuscitation and damage control surgery are increasingly performed with permissive hypotension (especially when there is no traumatic brain injury). Crystalloid usage is not encouraged in such circumstances. The technique involves a lower mean arterial pressure than normally tolerated in the hope that less hydrostatic pressure will reduce haemorrhage. A secondary benefit may be that as a result, if less crystalloid is given to increase blood pressure then less haemodilution will occur. It must be acknowledged that the evidence for reduced systolic blood pressure reducing bleeding is not conclusive and that hypotension in traumatic brain injury is associated with worse outcome.

Acute normovolaemic haemodilution (ANH)

The evidence for this method is limited. Small studies have shown a modest benefit in terms of blood loss and transfusion, but widespread employment of this technique has been limited by concerns of increased bleeding due to dilution of clotting factors, iatrogenic reduction of low oxygen delivery and resulting ischaemia.

Intrathoracic pressures

PEEP increases intrathoracic pressure and reduces venous return which may increase venous blood loss. In cases of increased bleeding, positive intrathoracic pressure could be reduced so long as it did not impact on oxygen saturations.

Positioning

Having the operative site above the level of the heart can reduce blood loss by enhancing venous return; however, the risk of venous air embolism must be considered. In the prone position for spinal surgery, avoidance of abdominal compression not only decreases respiratory compromise and risk of organ trauma, but also reduces venous shunting through the epidural veins, lessening venous bleeding.

Regional anaesthesia

Regional anaesthetic techniques may be effective in the reduction of operative blood loss; meta-analysis of studies addressing blood loss in joint arthroscopy suggest that allogeneic transfusion may be reduced in hip but not knee arthroplasty. In other surgical procedures, including hip fracture, peripheral vascular, retropubic prostatectomy, caesarean section and bowel surgery, blood loss was significantly reduced, but did not reduce transfusion rate when liberal transfusion targets are used. Many of the studies, however, preceded the routine use of tranexamic acid, and hence the outcomes may lack significance in current practice.

Antifibrinolytic therapies

These inhibit the clot-dissolving fibrinolytic pathway and most widely available of these are tranexamic acid and aprotinin.

Tranexamic acid: this lysine-derivative blocks the binding site of plasminogen activator, inhibiting fibrinolysis. This has come into vogue as a result of the CRASH-2 trial where early (within 3 hours) administration of tranexamic acid (TXA) reduced mortality due to bleeding in trauma patients.[6]

Clinically, tranexamic acid administered during major trauma mirrors the doses given during the trial: 1 g as a bolus IV followed by a further 1 g as an infusion over 8 hours.

Concerns related to thrombotic complications appear unsubstantiated. TXA usage is now standard practice during hip and knee arthroplasty; both procedures identified as high risk of thrombo-embolic complications, but TXA has not been associated with increasing the incidence of these events.

High doses of TXA are necessary to increase the risk of neuroexcitation and seizures, and are only seen when doses exceed 100 mg/kg/day.

Aprotinin: a bovine pancreatic trypsin inhibitor is a serine protease inhibitor which, at lower doses acts on plasmin, inhibiting fibrinolysis. At higher doses it reduces coagulation via kallikrein inhibition. This drug was commonly used in cardiac surgery, where it had been shown to reduce blood loss; a small evidence base exists for use in orthopaedic and hepatic transplant surgery. Following the 2007 BART study, the drug was voluntarily withdrawn on account of increased mortality and renal failure; however, it has been re-licenced for use in myocardial revascularization.[7]

Monitoring coagulation function

Point-of-care testing and its role in avoiding intraoperative blood transfution

Thromboelastography (TEG) and thromboelastometry (TEM) are forms of point-of-care testing (POCT) that analyse the global coagulation state. With the advent of the cell-based model of coagulation, the role of these viscoelastic devices is becoming increasingly relevant to clinical practice.

POCT may be used in the theatre setting to provide near real-time data of haemostatic function. A recent Cochrane review has suggested that utilizing a transfusion strategy guided by these tests could both reduce the use of intraoperative blood products, as well as reduce the morbidity in patients suffering haemorrhage.[8]

Having POCT results allows the clinician to promptly review multiple aspects of coagulation function and to make therapeutic inferences from them. In many organizations, treatment algorithms guide clinical response. Distinct benefits therefore exist over the time inefficient alternative of waiting for laboratory results which may not provide key information or using clinical acumen alone to optimize coagulation.

POCT is not without drawbacks; it remains an in vitro test and therefore does not take into account the effect of endothelium on coagulation. Use of POCT devices necessitates that all staff using such devices undergo appropriate training and that the devices undergo regular (often daily) quality assurance tests. At the time of writing tests for DOAC activity are not available for clinical use.

How TEG works

TEG works by measuring the torsion created when a pin is rotated in a cup of whole blood. Throughout the process of clot formation and breakdown, a torsion wire connected to a mechanical/electrical transducer undergoes a change in signal strength that is represented numerically and graphically.

Common metrics from the process include:

- **R (reaction) time** represents the lag from the start of the test until initial fibrin concentration. It is affected by the levels of clotting factors in the plasma.
- **K (kinetic) time** is the time taken to reach a certain level of clot strength (20 mm amplitude).
- **Alpha angle** measures the speed at which fibrin accumulation and cross linking takes place.
- **Maximum amplitude (MA)** represents the stability of the clot. It is affected by platelet number and function, as well as fibrinogen concentration.
- **CL30 and CL60.** provide measures of clot lysis time from the MA. They indicate clot stability and fibrinolysis.

NICE guidance: the role of POCT

In 2016, NICE published guidance around major trauma that made recommendations for research into the cost effectiveness and clinical utility of point of care coagulation testing. It was acknowledged that TEG/ROTEM may provide a more prompt change from fixed ratio blood products replacement protocol to targeted treatment of coagulopathy when compared with traditional laboratory studies. The additional cost of POCT devices may be offset by both a reduction in blood product use and improved patient outcomes.

Consideration of a restrictive transfusion strategy

The use of allogeneic (donor) transfusion will increase the haemoglobin concentration and hence the oxygen carrying capacity of the blood (except in situations where ongoing-bleeding exceeds the rate of transfusion). It does not follow, however, that use of allogeneic red cells improves outcome in surgical patients. Stored red blood cells (RBCs) do not function as well as circulating RBCs, affect immunological function and may contain significant concentrations of free haemoglobin. The benefits of increased oxygen delivery and other red cell function must be balanced against the risks associated with allogeneic RBC transfusion. Restrictive transfusion, with a threshold of 70 g/L, is considered appropriate in most clinical situations with a number of studies demonstrating no detriment to outcome when comparing liberal to restrictive transfusion triggers. Carson et al. concluded that patients subject to a restrictive transfusion policy do not suffer adverse effects in terms of mobility, myocardial infarction, death and length of stay when compared to their liberally transfused counterparts.[9]

It is of paramount importance to understand that restrictive triggers should only be used in the haemodynamically stable patient. It is very difficult, therefore, to use these triggers in the situation of the bleeding patient in theatre.

No difference in outcome has been demonstrated between restrictive and liberal transfusion within fracture neck of femur surgery.

However, not all evidence supports restrictive transfusion. Murphy et al.[10] reported that restrictive transfusion resulted in a worse outcome when compared to liberal RBC transfusion in cardiac surgical patients. The decision whether or not to transfuse therefore requires the clinician to respond to the individual clinical situation, appreciating that serious adverse effects upon morbidity may not be witnessed immediately; the clinician should consider the risk-benefit for each unit that is administered.

A number of trials that have considered liberal versus restrictive transfusion have reported significant cross over between the two study groups (e.g. FOCUS and TiTRE 2); one inference from this may be that the haemoglobin concentration value may not be best indicator of acceptable cardiovascular stability.

Intraoperative cell salvage (ICS) (Figure 1)

Autologous blood transfusion has become a more common intervention to avoid permissive anaemia, hazards of allogeneic blood transfusion and associated blood storage lesions and may also be acceptable to patients who refuse allogeneic transfusion.

It involves harvesting blood from the intraoperative site and from wound swabs via a specialized suction device. The suction device has two lumens: one removes blood from the surgical site, the other adds a pre-determined volume of anticoagulant to the point of blood collection. Heparin or citrate can be used. Anticoagulant is added to the blood to dilute by around 15%. The mixture is then filtered to remove large debris e.g. bone and clots, and collected in a reservoir. Red cells are separated from the substrate by various techniques, the most common being centrifugation. This removes waste products and red blood cells remain with a high haematocrit. The red cells are then washed with and stored in a suspension of 0.9% saline. The product is then re-infused into the patient within 6 hours of processing.

During processing, anticoagulant, clotting factors and platelets are all removed; therefore the reinfusion bag contains only red blood cells suspended in saline (with a haematocrit of between 40% and 60%). In large-volume blood loss, clotting factors, cryoprecipitate and platelets will commonly be required When ICS is used in major haemorrhage situations, the ratios of 1:1 for red cells to plasma (thawed FFP) should be used, hence

Cell salvage and transfusion

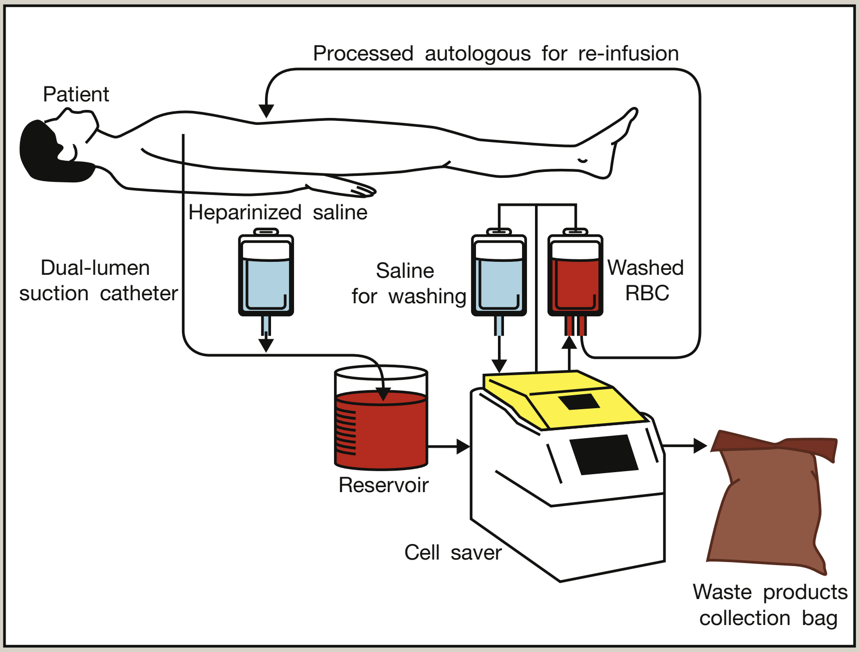

Figure 1

the volume of ICS blood should be considered as well as the volume of donor red cells administered.

Filters

There are numerous filters available for use with cell salvaged blood. A standard 200 μm blood administration screen filter is sufficient in most clinical situations.

- **Leukocyte depletion filters (LDFs):** these are affinity filters, which have a charged surface, attracting negatively charged leukocytes. Important considerations are the much reduced flow rate, the maximum capacity of the filter (volume before charge is eliminated and filter must be changed) and a MHRA safety alert reporting several episodes of hypotension associated with use of an LDF. They have been shown to significantly reduce (but not eliminate) the presence of tumour cells when ICS is used in malignancy surgery.
- **Lipid reduction filters:** salvage substrate may contain significant concentrations of lipid, especially during orthopaedic surgery and spinal deformity surgery. During the collection process, lipid deposits may coalesce and as a result be drawn into the reinfusion product. Lipid reduction filters are therefore used in this context to minimize infusion of the lipid material.

Newer machines now offer fat reduction cylces which remove nearly all the fat from the re-infusion product.

Indications for cell salvage

- Surgery where blood loss is expected to be 500 ml or 10% of circulating volume.
- Major haemorrhage.
- Patients who will not accept allogeniec blood transfusions.
- Blood cross-matching difficulties where donor blood may not be readily available.

Systematic review has shown that intraoperative cell salvage has been effective in cardiac, vascular and orthopaedic surgery, reducing the absolute risk of requiring a blood transfusion by 21% without causing adverse effects.[11]

Contraindications to ICS (absolute)

- Aspiration of toxic materials or solutions e.g. non-set cement, topical haemostatic agents, hydrogen peroxide, hypotonic wound irrigation, topical antibiotics, iodine.
- Patient refusal
- Aspiration from metallosis contaminated tissue.

ICS use in situations that require special consideration:

1. Bacterial infection: aspiration of frank pus or faecal material may result in high concentrations of viable bacteria and should be avoided. In vitro studies of ICS in animal models from a soiled abdomen suggest no increased incidence of systemic sepsis. Literature on the use of ICS in the trauma abdomen is lacking and the safety of the technique in the contaminated abdomen unknown. ICS produce consistently contains skin bacteria; however the incidence of sepsis or wound infection is not increased. The use of prophylactic antibiotics may have protective effects on infection rates.

2. Malignancy: ICS in malignancy surgery may offer benefit by reducing the need for allogeneic transfusion, hence reducing transfusion related immunomodulation (TRIM). A meta-analysis of ICS in malignancy surgery has demonstrated no detrimental effect of ICS upon patient outcome when compared to allogeneic transfusion or preoperative autologous donation (PAD). Reduction in substrate tumour load is recommended by targeted suction, wound irrigation and suction to waste. Tumour load can further be reduced by use of a LDF, though viable tumour cells may still exist in the infusate.

Donor transfusion in bowel cancer surgery has been demonstrated to have detrimental effects upon all outcome markers when compared to no transfusion.[12]

Malignancy has been deemed an absolute contra-indication by some authors unless the product is irradiated prior to reinfusion. Despite this, ICS is used in malignancy, with NICE guidelines in radical prostatectomy.

Updated UK guidelines for ICS in clinical practice advise that the use of ICS in infected or malignancy procedures should be discussed on a case to case basis, and the risks of alternatives be considered when making the decision. The patient should be informed of the risks and benefits of the alternatives when ICS is to be used in this context and specific consent attained.[13]

3. Haemoglobinopathies:

Sickle cell (SCD) — the washing of red cells has the potential to cause sickling or lysis of salvaged cells in SCD and trait. There are no trials in this setting but a number of case reports have reported successful use. However in others, testing of product revealed significant sickling and the blood was rejected prior to administration. Exchange transfusion in sickle cell disease is used to reduce the risk of crisis, hence in this particular situation, allogeneic transfusion may have specific benefits relating to peri-operative care, it is advised that such situations are discussed with the regional haemoglobinopathy specialist team.

β-***Thalassaemia*** — increased red cell fragility is associated with extracorporeal haemolysis; this has led to cautions in its use, though ICS has been used without complications. In caesarean section for placenta accreta. Estimation of free haemoglobin in salvage product, prior to re-infusion should be considered.

4. Cell salvage in obstetrics: ICS during caesarean section (CS) has become standard in many centres, though theoretical concerns relating to contamination with neonatal red cells and amniotic fluid embolus (AFE) exist. The Salvo trial concluded that a modest benefit was seen when ICS was used in elective CS. The UK guidelines have concluded that ICS should not be routinely used in elective CS.[13] RhD antibody generation is a concern for the RhD-negative mother due to the risk of haemolytic disease of the fetus and newborn in subsequent pregnancies. In cases of cell salvage the recommendation is that if the RhD type of the baby is unknown or confirmed RhD positive then a minimum dose of 1500 IU anti-D Ig should be administered following re-infusion of salvaged red cells. An estimation of feto-maternal haemorrhage (FMH) 30-45 minutes after reinfusion and further anti-D Ig administered as determined by the FMH. If the Kleihauer method was used for this estimation a confirmatory flow cytometry quantification should be performed by the regional referral centre.

AFE as a disease entity is difficult to diagnose, and the role of the neonatal squame unclear. LDFs are almost always used and are effective at reducing squame load in the ICS product, again their use is not universal in CS.

Jehovah's Witnesses (JW): blood is regarded as sacred and transfusion of blood or its components are not normally acceptable to JW patients undergoing surgery. Many carry a signed and witnessed advance directive absolutely refusing blood products and releasing doctors from liability.

Haemodilution and intraoperative cell salvage may be acceptable when the circuit is in continuity with the patient's own body and in a continuous flow system. This may be achieved by priming the circuit with saline, commencing a slow infusion to ensure cannula patency and attaching a three way tap between the salvaged product and the patient's cannula. The three-way tap will allow the introduction of an LDF without breaking the circuit. ◆

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Acknowledgements

The authors gratefully acknowledge the contribution of Dr Christopher Hamilton to the previous edition of this article.