

Anaemia and blood transfusion: incorporating patient blood management

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Abstract

Both red blood cell (RBC) transfusion and anaemia or low haematocrit increase morbidity and mortality associated with surgery. Chronic anaemia in the elective patient carries a small risk in non-haemorrhagic surgery. Where bleeding is anticipated anaemia should be treated medically to avoid (RBC) transfusion which will increase the risk to the patient. Major bleeding (MB) has the biggest impact on adverse outcomes. Acute anaemia is caused by surgical bleeding and requires RBC transfusion to keep the haematocrit (Hct) above 21% and haemoglobin (Hb) above 7 g/dl in patients without coronary artery disease (CAD) and between Hct 24–27% or Hb >8 g/dl in patients with CAD. Having a patient blood management programme can mitigate the problem. Medical, surgical and anaesthetic planning are paramount to avoid bleeding and transfusion which together have a significant impact on adverse outcomes for the patient.

Keywords Anaemia; blood transfusion; haemorrhage; patient blood management; surgery; transfusion trigger

Background

In 1628 William Harvey published a description of the human circulation. This laid the foundation for the concept of blood transfusion. Animal transfusion followed but human transfusion was banned until Dr James Blundell successfully transfused an obstetric patient in 1818. The discovery by Landsteiner of the four blood groups followed in 1901. Although the first blood donor service was established in 1920 by the British Red Cross, routine blood transfusion is a recent medical phenomenon. Throughout much of modern medicine, blood was given to save life with little thought to the longer-term consequences. Blood is readily available now and we transfuse more frequently, but saving life remains the principal indication.

Aim

This article will focus on the management of anaemia for surgical patients and the impact of anaemia, bleeding and blood

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transfusion on outcomes. It will also cover patient blood management (PBM).

It will concentrate on data from orthopaedic, cardiac and cancer surgeries as these consume most of the red blood cells (RBCs) transfused. The focus is on allogenic blood rather than clotting factors. We will address the questions:

1. Is preoperative anaemia a risk factor for adverse events?
2. Does correcting the anaemia remove the risk?
3. Can we distinguish between the adverse outcome caused by anaemia or RBC transfusion?
4. Is there a single haematocrit (Hct) or haemoglobin (Hb) level at which transfusion is indicated?
5. Does chronic preoperative anaemia have the same risk as intra-/postoperative anaemia?
6. Can patients with cardiac disease, mainly coronary artery disease (CAD), be managed in the same way as patients with non-cardiac disease?
7. Does RBC transfusion cause harm in the short or in the long term?
8. Is transfusion good for the patient?
9. Can we distinguish between harm caused by haemorrhage and harm caused by RBC transfusion?

Preoperative anaemia

The World Health Organization defines anaemia in men as Hb <13 g/dl and in non-pregnant women <12 g/dl. Using these definitions, about 25–30% of patients over 65 years having surgery in Europe and the USA are anaemic. Iron deficiency anaemia (IDA) is the leading cause of anaemia worldwide, although in the West, anaemia of chronic disease accounts for a large proportion. Though defined differently by gender we do not distinguish when it comes to transfusion thresholds perioperatively. Anaemia is a very strong predictor for receiving a blood transfusion but does not always predict the need for transfusion, e.g. chronic anaemia alone is not an indication for transfusion.

Should the preoperative anaemic patient be postponed, transfused or just treated as normal?

If the Hb is above 10 g/dl the issues to consider are expected blood loss and CAD. When blood loss is predicted to be low there is no benefit to the patient in giving blood. If these patients are compared with a non-anaemic patient the outcome will be worse according to the pathology associated with anaemia. The main adaptive mechanism to chronic anaemia is via 2,3 diphosphoglycerate (2,3 DPG). This decreases the affinity of oxygen (O₂) to haemoglobin thus promoting release at the tissues (Figure 1). Levels of 2,3 DPG are low in stored blood which reduces the efficacy of acute transfusion though haemoglobin still carries O₂. The Bohr effect is an acute change to shift the oxyhaemoglobin curve to the right, thereby increasing oxygen delivery to the tissues in the presence of acidosis. During surgery attention is therefore needed to maintain normothermia and normal pH.

The Poiseuille formula and knowledge of blood rheology is also relevant to understanding the risks and benefits of both anaemia and transfusion. Figure 2 shows the physics of flow/viscosity and suggests an optimal Hct of 25–30%. However the optimal Hct can change not only in illness but also in health (e.g.

childhood, pregnancy) but also varies with different pathophysiology states.

Somewhat surprisingly, a lowest safe limit of Hb/Hct is not known. Information from healthy volunteer studies suggests that at a Hct of 15% asymptomatic ECG changes occur,¹ while in cohort studies of Jehovah's witnesses, as Hct falls below 21% mortality increases, particularly with extreme acute anaemia (Hct below 10%), which was associated with 50% mortality²

One major variable that alters acutely in major haemorrhage is cardiac output (CO) (Figure 3). A diminished oxygen supply will increase CO. This adaptive mechanism can increase O₂ carrying capacity fourfold or fivefold at the expense of increasing myocardial O₂ demand, which explains why the threshold for patients with CAD is higher and why fit young patients without CAD can survive extreme anaemia (e.g. Hct of 7%).

In the elective patient the need for preoperative intervention should therefore be based on an estimate of whether expected blood loss will cause organ hypoxia and ischaemia. Anaemia is a marker for many diseases and should always be investigated before treatment is started. Anaemia should if possible, be corrected preoperatively.

Preoperatively there are usually three treatment options.

- 1. Iron alone.** About half of anaemic patients will have measurable IDA. Many of the rest, having anaemia of chronic disease, will have functional IDA. It has been shown that many of these patients will respond to iron therapy. Unfortunately, oral iron is poorly tolerated, and intravenous is more reliable (see below).
- 2. Iron plus erythropoietin (EPO).** Within 5 days of treatment, EPO will cause red cell proliferation. It has been shown to increase Hb and reduce transfusion in cardiac and orthopaedic surgery but not colorectal surgery. There are safety

concerns with cancer and thrombotic events. Many dialysis patients will be on EPO. For a general surgical population, its use should be considered on an individual basis. Supplemental iron (and possibly folate/B12 in selected cases) is required.

- 3. Blood transfusion.** Giving packed red blood transfusion preoperatively is currently the most common method for treating preoperative anaemia. It can correct anaemia immediately before surgery. There is some correction of 2,3 DPG, temperature, potassium and pH but volume overload is possible.

Current UK 'National Patient Blood Management' recommendations for treating preoperative anaemia include iron and PBM, but not EPO.³

Risk associated with preoperative anaemia

Multiple large studies demonstrate that anaemia is an independent risk factor for poor outcomes, including death, wound infections, thrombosis, and multiple organ dysfunction.⁴

Does treating preoperative anaemia reduce the risk?: studies in cardiac and non-cardiac patients show preoperative treatment with iron and EPO not only increases preoperative Hb but also reduces transfusion and morbidity compared to non-treated patients.^{5,6}

Anaemia with or without blood transfusion

A number of studies have shown that generally, in both the short and long term, moderate to severe anaemia is independently associated with worse outcomes. Preoperative anaemia is a significant risk in determining long term survival. Mild anaemia without transfusion has the same outcome as for non-anaemic patients. Figure 4 shows that the requirement for perioperative transfusion increases the risk at every level of anaemia. This effect⁶ is particularly seen in cancer surgery. Anaemia and blood transfusion increase adverse events but the impact of bleeding is difficult to separate out, and outcomes in general are worse than those seen non-cancer surgery.^{7,8} The same principles for blood management apply. Tumour recurrence does not seem to be affected by transfusion.

Acute anaemia during surgery

As a general principle, the best outcomes are seen in patients without anaemia who are not transfused. Adaptive⁹ responses to chronic anaemia may allow patients to tolerate anaesthesia and surgery, but the margins for safe acceptable blood loss will be reduced. Operating on patients who require transfusion during surgery will expose them to increased risk. Allowing them to become anaemic before transfusing is an additive risk.

At some point, ischaemic risk outweighs the risk from RBC transfusion – this should be regarded as the transfusion threshold.

Acute anaemia is caused by haemorrhage and is a dynamic situation. The Hct should not reach critical levels before transfusion is started. Clinical skill and judgement are required to assess the situation. The Hct should be checked before giving blood. Volume replacement with crystalloid/colloids should be proportionate to maintain normovolaemia which is an important part of the acute response to increase cardiac output (Figure 3).

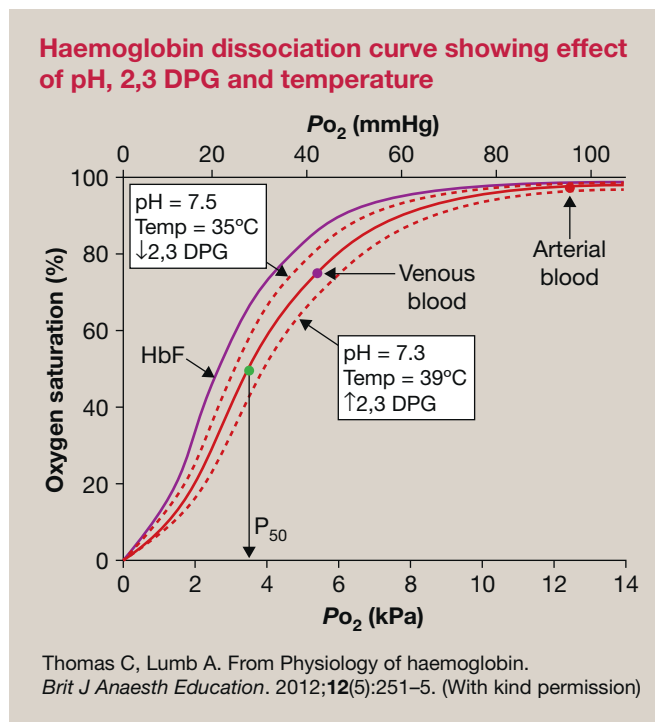


Figure 1

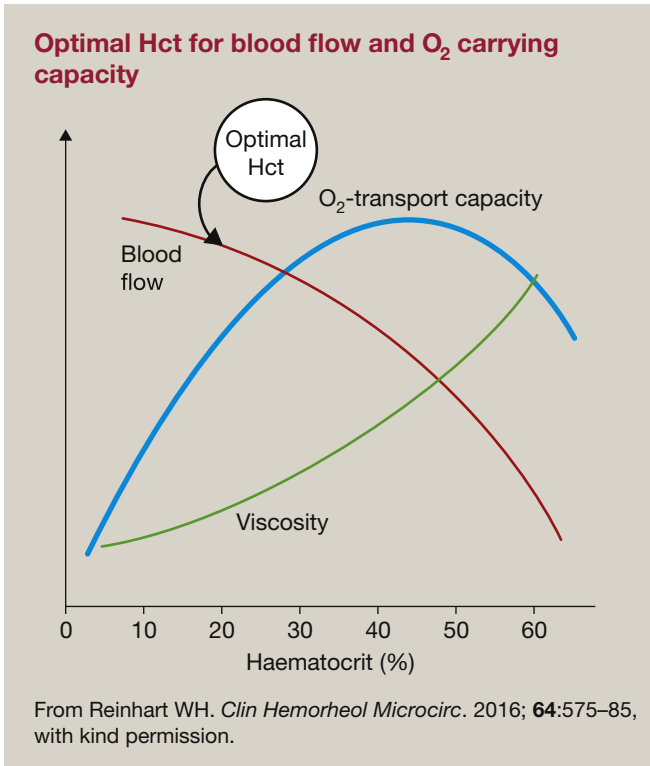


Figure 2

When blood loss is controlled and measurable a simple calculation as in Figure 5 can be used as a guide to how much allowable blood loss is required to produce a given Hct. At this point the Hct can be checked and a transfusion decision made. The example shows that significant amounts of blood can often be lost if normovolaemia is maintained.

The UK Blood Transfusion Service and the American Association of Blood Banks guidelines recommend transfusion should be considered if the haemoglobin is 8 g/dl or lower. Jehovah’s Witness patients can survive extreme anaemia (Hb of <5 g/dl),

although such extreme anaemia carries high morbidity and mortality.

Relative impacts of acute anaemia, haemorrhage or blood transfusion

Anaemia and blood transfusion both have risks. Major bleeding also poses risk to patients. It is difficult to disentangle the relative risks of MB and blood transfusion. The TITRe2 and TRICS studies compared transfusion thresholds of around 7.5 g/dl (restrictive) and 9–9.5 g/dl (liberal) in perioperative cardiac patients. In the TITRe2 study, there was some transfusion benefit in the liberal group, although this study was limited to postoperative transfusion only. The more recent and extensive TRICS study¹⁰ (perioperative practice with longer follow-up) showed no benefit in a liberal transfusion strategy. Overall, recommendations are that a restrictive policy (Hb 7.5 g/dl or Hct 23%) is safe in cardiac surgical patients.

Does patient age matter?

A number of studies into the relationships between patient age and transfusion outcomes have produced conflicting results. At present, insufficient information is available to use different transfusion thresholds based on age alone.

Haemorrhage

Data from the UK National Cardiothoracic Surgical database show that blood loss greater than 1000 ml and blood transfusion of greater than two units were associated with worse outcomes than lower losses or no transfusion, even for urgent cases.

Major bleeding and transfusion have an additive effect on poor outcomes (Figure 6).¹¹ This is linked to disease severity and surgical techniques. Also acute blood loss, even if the volume is not enough to drop the Hct to threshold levels, can cause harm in itself.

Do we transfuse at a fixed Hct/Hb trigger?

Although epidemiological Hct/Hb triggers are widely used especially when monitoring is limited, physiological end-points

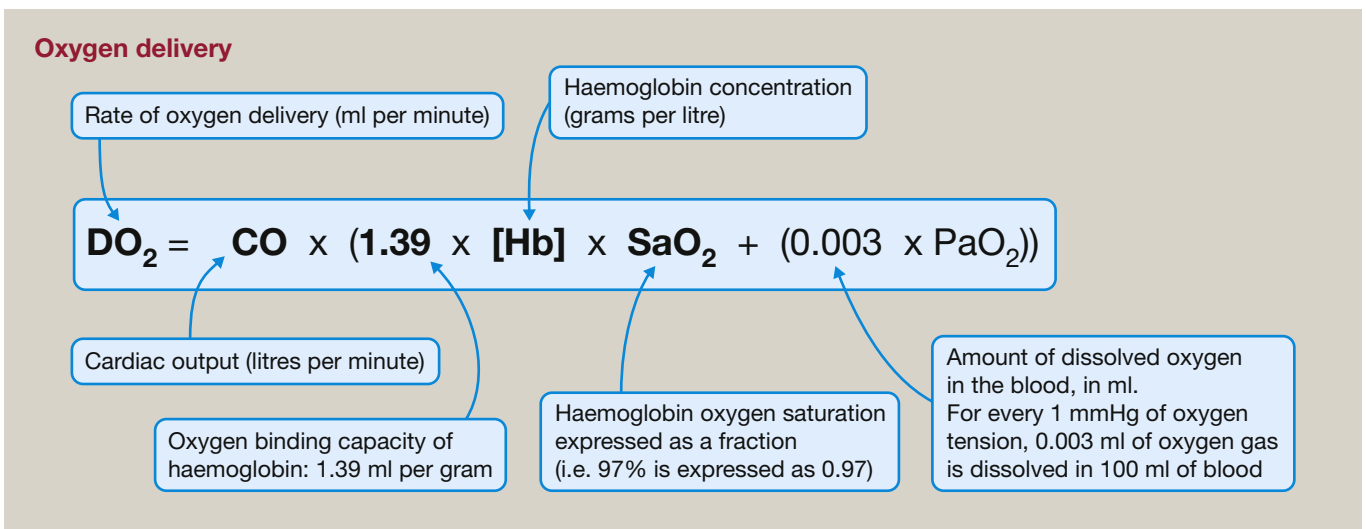


Figure 3

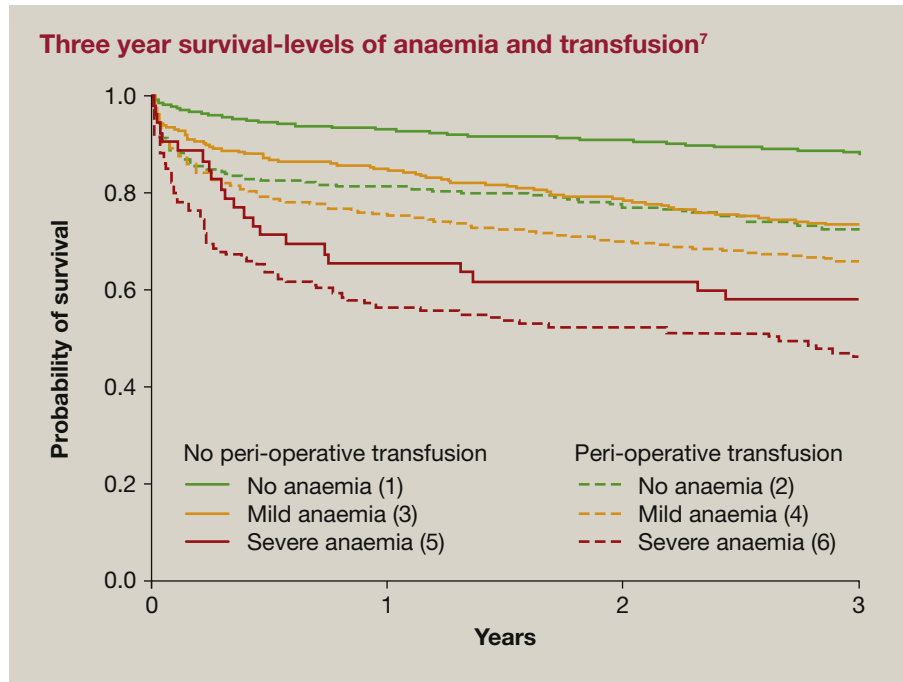


Figure 4

Formula and calculation to estimate allowable blood loss

$$\text{Allowable blood loss} = \text{BV} \times \frac{(\text{Hct}_i - \text{Hct}_t)}{\text{Hct}_i}$$

Hct_i = Initial haematocrit
 Hct_t = Target haematocrit
 Blood Volume (BV) = weight (kg) x 75 ml

Example:
 Allowable blood loss = $\frac{(70 \times 75) \times (40_i - 27_t)}{40_i}$
 Hct_i = 40% Hct_t = 27% BV = 70 kg x 75 ml
Allowable blood loss = 1700 ml

Figure 5

may help to identify the exact trigger for an individual patient. Perioperatively, most blood is given based on measured Hb/Hct and witnessed bleeding, not on any other objective signs. Based on multiple studies and expert consensus statements, recommended transfusion triggers are currently¹²

- Hb 8–10 g/dl or Hct 25–30% in patients with cardiac disease.
- Hb 7–8 g/dl or Hct 21–24% in non-cardiac patients.

Physiological end-points that help with individual patients to avoid ischaemic injury

Over the years, multiple monitoring devices have been used to estimate blood volume, fluid responsiveness, blood loss, and

tissue perfusion or oxygenation. Each device has strengths and weaknesses, but there is no single monitor that reliably allows clinicians to routinely determine the exact physiology of, and best management for, an individual patient is. Clinical judgements are therefore based on a combination of tools. Some of the monitoring systems currently used to help assess perfusion and oxygen delivery (and therefore need for transfusion) are listed in Table 1.

Patient blood management

A preoperative haemoglobin (Hb) level of <12 g/dl can triple the risk of RBC transfusion. Thus, correcting preoperative anaemia to a Hb >12 g/dl is important. Low Hb is a modifiable risk factor for RBC transfusion. All patients at risk of blood loss during surgery should be entered into a PBM programme. Key principles of PBM (known as the three pillars) are: (1) optimizing the patient’s own blood elements including red cell mass; (2) minimizing the patient’s blood loss and bleeding; and (3) optimizing anaemic tolerance.

Preoperative period

Patients should be assessed at least 30 days prior to surgery to detect and treat the underlying cause of anaemia (most commonly IDA or anaemia of chronic disease). Severe anaemia is a relative contraindication for elective surgery and should be corrected.

Drugs that effect haemostasis: patients should have a multi-disciplinary review to weigh the risks and benefits of suspending therapy. There are likely to be institution specific differences between detailed management. See Table 2 for one example.

Pharmacological treatment of anaemia: *Iron:* perioperative iron administration can reduce the degree of anaemia and reduce

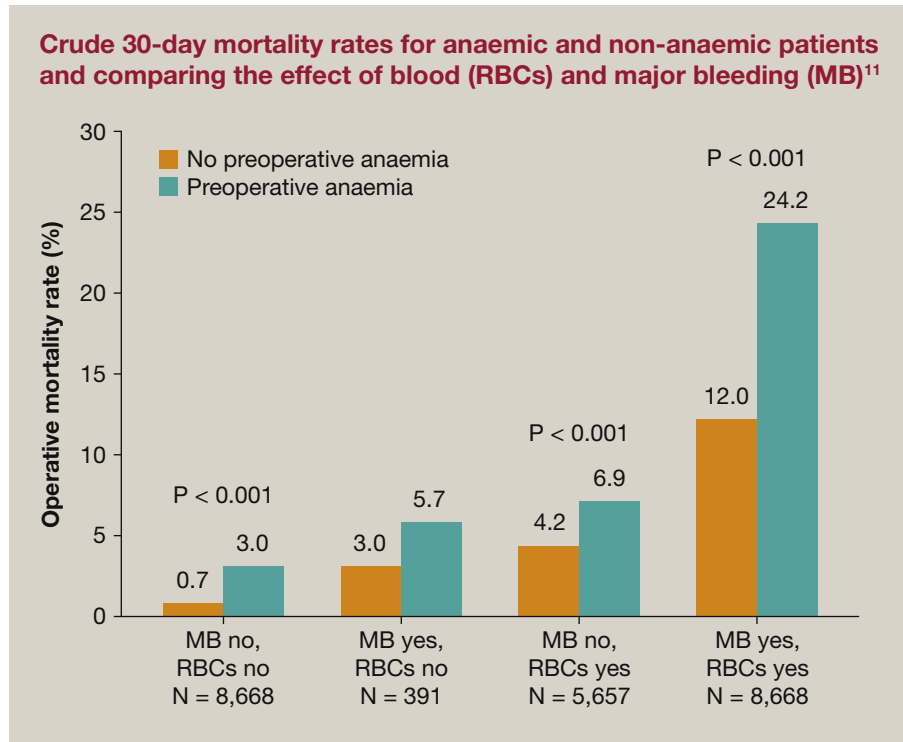


Figure 6

transfusion. The effect is greatest in those with more severe anaemia. Table 3 shows indications for Iron administration in the perioperative period.

Oral or intravenous iron?: The choice between IV and PO depends on the clinical situation, availability and cost. Problems with severe toxic reactions and anaphylaxis initially limited the

use of parenteral iron, but newer formulations are safer, e.g. iron sucrose, iron carboxymaltose. Oral iron is cheap and effective but the side effects cause poor compliance. Hepcedin is a regulatory hormone responsible for iron absorption. It is up-regulated in many inflammatory and bowel conditions which reduce iron absorption and availability.

Oral iron, even 30 days preoperatively is less effective than parental iron, given 10 days preoperatively. Parenteral iron allows full-replacement in one or two doses, depending on the product Table 4. In contrast, it has been estimated that the maximum amount of oral iron that can be absorbed is 25 mg/day. Parental iron given nearer the time of surgery will help with recovery but less effective in reducing intraoperative transfusion.

The use of parenteral iron in acute infection is not recommended.

EPO in perioperative period: EPO can be used to optimize autologous donation and particularly in patients for elective surgery with a rare blood group, transfusion refusal or difficult alloimmunization. However, it can increase thrombotic risk, and may shorten overall survival and increased risk of tumour progression or recurrence. Various treatment regimens have been described depending on the surgery involved.

Non-pharmacological treatment: Blood conservation strategies can be used to minimize RBC transfusion. Acute normovolaemic haemodilution (ANH) and preoperative autologous donation (PAD) are possible, but have a number of limitations which make them unsuitable for widespread routine use.

Intraoperative period

Pharmacological techniques and haemostatic agents: anti-fibrinolytics such as tranexamic acid or epsilon-aminocaproic

Monitoring perfusion and oxygen delivery		
Parameter	Details	Notes
ScVO ₂	Saturation of mixed venous blood in SVC.	Trending values <60% usually denotes impaired oxygen delivery. Transfusion may help if Hb/Hct low.
Serum lactate	Level of lactate in arterial or venous blood	Represents inadequate perfusion rather than oxygenation. No direct link with transfusion requirement
Arterial acidosis	pH/base deficit in arterial blood	Non-specific indicator of poor perfusion
Regional cerebral oxygenation SrO ₂	Regional O ₂ supply/demand for brain. Can be measured with non-infrared spectroscopy	Value <57% during Cardiopulmonary bypass may indicate impaired oxygen delivery. May be used as part of a transfusion protocol

Table 1

Drugs that affect haemostasis - use and reversal

Medication name	Cardiac surgery preoperative hold	In non-cardiac surgery preoperative hold	For urgent surgery (reversal)
Antiplatelet			
Aspirin	To continue	7 days	
Clopidogrel	5 days	7 days	FFP can be used
Prasugrel	7 days	10 day	
Ticagrelor	3 days	5 days	
Anticoagulant			
Warfarin	5 days		Vitamin K ⁺ (2–5mg), PCC
DOAC	48 h for major surgery, 24 h for minor surgery (with normal renal function)		<ul style="list-style-type: none"> • PCC for all¹³ • Idarucizumab for dabigatran • Andexanet alfa for others
Unfractionated heparin	2–6 h for IV, 12–24 h for SC		Protamine
Enoxaparin	24 h prior to surgery		Protamine (partially)
Others			
Selective Serotonin reuptake inhibitor	Discontinue therapy three weeks prior to surgery in patients undergoing high-risk procedures		
NSAIDs	For short acting (e.g ibuprofen) discontinue 24 h For long acting discontinue at least 3 days prior to surgery		

DOAC, direct oral anticoagulant (e.g. apixaban, rivaroxaban, dabigatran); IV, intravenous; SC, subcutaneous; NSAID, non-steroidal anti-inflammatory drug; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

Table 2

Indications for iron administration in the perioperative period

- In iron deficiency anaemia with suboptimal iron store (ferritin <100 mcg/L) or where significant blood loss is expected
- In anaemia of chronic disease oral (PO) or IV iron can be given in conjunction with EPO- see below
- early PO iron therapy is not clinically effective in postoperative anaemia. Routine use is not recommended

Table 3

acid can be used preoperatively, intraoperatively and post-operatively. Regimes vary with type of surgery. Topical agents (e.g. fibrin glue) may also reduce transfusion requirements.

Operating room techniques: meticulous surgical technique (including laparoscopic, thoracoscopic and robotic approaches) are a key factor in reducing perioperative transfusion. Hypotensive anaesthesia, adequate intraoperative warming, intraoperative cell salvage, point of care testing (e.g. thromboelastography) and active

coagulopathy management can also reduce transfusion requirements.

Postoperative period

Up to 90% of patients undergoing major surgery become anaemic postoperatively. Postoperative blunted erythropoiesis is a key factor, in addition to haemodilution, nutritional deficiency and pharmacological interaction. Management of anaemia in the postoperative period includes monitoring and treatment with IV

IV iron preparations

	Iron sucrose	Ferric carboxymaltose	Iron dextran
Dose	Multiple doses of 200–300 mg	≥50 kg: 750 mg IV x2 doses, min 7 days apart <50 kg: 15 mg/kg IV x2 doses mi 7 days apart	Multiple doses of 100 mg or single dose 1000 mg (in 250 ml saline) over 1 hour.
Maximum per dose	500 mg	1000 mg	1000 mg
Test dose	Not required	Not required	Required

Table 4

iron \pm EPO and continuing a restrictive transfusion threshold. The risk/benefit of blood remains in favour of transfusion at a threshold Hct 21% in patients without CAD and at 24% in patients with CAD, but no higher. Avoiding MB and transfusion is clearly better for patient outcome.

Future prospects

Preoperative therapy for anaemia will be more widespread and cheaper. It will not be acceptable to present an anaemic patient for elective major surgery.

Monitoring organ-specific ischaemia will allow patient-specific transfusion when a major organ is compromised.

Refinements in surgical technique and awareness of the dangers of bleeding will reduce transfusion requirements.

Conclusion

Perioperative anaemia is important, is amenable to treatment, and if appropriately managed, can save lives. There are enough large studies to support an overall approach to perioperative management which reduces intraoperative bleeding and RBC transfusion thus improving outcomes. Certain physiological measurements can be used to individualize the exact timing of when to give and not give blood for a specific patient. Conflicting results for some aspects of care in various studies arise because of the heterogeneous populations and surgical interventions used, and because of difficulty in separating anaemia (presence and degrees), transfusion (type and amount) and haemorrhage (timescale and volume). At present, a combined strategy of technical, planning, physiological and pharmacological approaches to reduce bleeding will be more likely to save lives.

In answering the original questions:

1. *Is preoperative anaemia a risk factor?* Chronic mild anaemia is well tolerated and carries a small risk. Acute or moderate-severe anaemia is a risk.
2. *Does correcting the anaemia remove the risk?* If done without blood it will reduce the risk associated with increased transfusion requirement. Correction with blood is an additive risk.
3. *Can we distinguish between the adverse outcome caused by anaemia or blood transfusion?* Both have a risk though blood transfusion may be the greater. And the combination carries additive risk.
4. *Is there a single Hct or Hb level at which transfusion is indicated?* Yes. Keep Hct above 21%, Hb 7.0g/dl in patients without CAD. Keep between 25 and 27% Hct and Hb 8.0–9.0g/dl in patients with CAD.
5. *Does chronic preoperative anaemia have the same risk as intraoperative or postoperative anaemia?* No. Chronic anaemia is well tolerated and can be corrected medically, reducing the need for transfusion. Intraoperative anaemia requires blood once the threshold is reached.
6. *Can patients with cardiac disease, principally CAD be managed in the same way as patients with non-cardiac disease?* No. patients with CAD require a higher Hct (approx. 25–27%). With close monitoring individuals patients may be safe at Hb 7.5 g/dl or Hct 23%.
7. *Does RBC transfusion cause harm?* Yes. Transfusion carries a risk in the short term. In the long term there is a degree of risk but this is ill defined.
8. *Is transfusion good for the patient?* Yes. If Hct is dropping below threshold for adequate oxygen carrying capacity, transfusion will decrease the risk of ischaemia.
9. *Can we distinguish between harm caused by haemorrhage and harm caused by transfusion?* Haemorrhage is the greatest risk. Consideration of surgical technique, complexity, control of medications and physiology should be employed to reduce bleeding. ◆

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