Preoperative anaemia

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Key points
Anemia is present in 5–78% of patients requiring a surgical intervention.
Anemia is an independent risk factor for adverse perioperative events.
All patients undergoing surgery should be assessed for anemia.
If detected, the cause of the anemia should be investigated and treated.
Correction of anemia conserves blood supplies and improves outcome.

Preoperative anaemia increases requirement for red blood cell transfusion and is independently associated with adverse outcome in patients undergoing both cardiac and non-cardiac surgery. Strategies to correct anaemia before surgery conserve blood stocks, improve outcome, and are integral to the Department of Health’s Enhanced Recovery Program and the World Health Organization’s (WHO) Patient Blood Management (PBM) guidelines. The aim of this article is to describe the significance of anaemia in preoperative patients, explain the pathophysiological consequences, and provide a structured approach to detection, evaluation, and management.

Significance
Anemia derives from the Greek ‘anaimia’ meaning lack of blood. Currently, there is no unifying definition of anaemia; however, two well-accepted classifications are the WHO and the National Cancer Institute (NCI) schemes (Table 1).

The reported prevalence of preoperative anaemia varies according to the population studied and the definition of anaemia used. Using a non-uniform definition of anaemia, estimates range between 5% in geriatric women with hip fracture to 75.8% in patients with Dukes stage D colon cancer. When defined according to the WHO classification, preoperative anaemia has been reported to affect 54.4% of patients before cardiac surgery and 39% of patients undergoing non-cardiac surgery. Evidence suggests that anaemia is more prevalent in patients with co-morbidities undergoing major surgical procedures. Preoperative anaemia is associated with adverse perioperative outcome. In the largest study to date, Wu and colleagues’ retrospectively reviewed 310,311 veterans aged 65 yr or older undergoing major non-cardiac surgery and found that a haematocrit <39% was associated with an increased risk of 30 day postoperative mortality and cardiac events. Analysis of data from 227,425 patients demonstrates that the detrimental effects of preoperative anaemia are not confined to the elderly but occur across all age groups and remain significant after adjustment for associated disease processes (including diabetes, systemic sepsis, cardiovascular, respiratory, hepatobiliary, renal, neurological, and haematological–oncological disorders). Furthermore, the risk of major non-cardiac complications (respiratory, urinary, wound, septic, and thromboembolic complications) is increased. Evidence is also emerging that preoperative anaemia has a negative effect upon functional recovery, length of hospital stay, and quality of life. The adverse impact of anaemia on perioperative outcome is potentially confounded by the receipt of autologous red blood cells, which are known to increase mortality and morbidity. However, information from patients who refuse transfusion for religious reasons and propensity score matching of observational data demonstrate that preoperative anaemia is an independent risk factor for adverse outcome.

Pathophysiology
Tissue oxygen delivery is determined by the oxygen content of the blood and the cardiac output (CO) as described by the formula:

$$DO_2 = CO \times (1.34 \times Hb \times S_aO_2 + 0.003 \times PaO_2)$$

The major proportion of oxygen contained within the blood is bound to haemoglobin, thus anaemia results in a significant reduction in oxygen delivery (Table 2). In response to anaemia, a series of compensatory mechanisms are activated in order to restore the supply of oxygen to the tissues:

(i) Increased oxygen extraction: tissues such as the kidney, skeletal muscle, and skin can increase the amount of oxygen they extract; this leads to an increase in total body extraction and a decrease in the mixed venous oxygen saturation. Organs that already have a high extraction ratio (e.g. brain and heart) are unable to compensate using this mechanism.
Preoperative anaemia

(ii) Redistribution and increase in CO: anaemia causes a decrease in the viscosity of blood, which reduces systemic vascular resistance and increases CO (Fig. 1). Sympathetic activation due to stimulation of chemoreceptors by hypoxaemia may also contribute. CO is also redistributed to organs with high oxygen demands (e.g. brain and heart).

(iii) Altered affinity of haemoglobin for oxygen: anaemia causes a rightward shift in the oxygen dissociation curve (ODC) (due to an increase in 2,3-diphosphoglycerate and hydrogen ions) which reduces the affinity of haemoglobin for oxygen and favours releases to the tissues at higher partial pressures (Fig. 2).

If these responses are insufficient to maintain an adequate supply of oxygen then the decrease in oxygen tension triggers a cascade of intra-cellular adaptations, orchestrated by hypoxia-inducible factor, which result in transcription of hypoxia-response genes, such as erythropoietin, vascular endothelium growth factor, and those that favour a metabolic switch towards the anaerobic utilization of glucose.

In the perioperative period, these compensatory mechanisms can be overwhelmed (Table 3); this results in an imbalance between oxygen supply and demand that predisposes to ischaemia and adverse perioperative outcome.

Clinical approach

Detection

Full blood count should be measured in accordance with the National Institute of Clinical Excellence (NICE) guidelines and in all patients in whom anaemia is suspected on the basis of history and examination. Ideally, this assessment is made at least 4 weeks before surgery in order to allow opportunity for full evaluation and institution of treatment.

Table 1. Definitions of anaemia according to the WHO and the NCI schemes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO</th>
<th>NCI</th>
</tr>
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<tbody>
<tr>
<td>Male Hb</td>
<td>&lt;13 g dl⁻¹</td>
<td>&lt;12 g dl⁻¹</td>
</tr>
<tr>
<td>Female Hb</td>
<td>&lt;12 g dl⁻¹</td>
<td>&lt;11 g dl⁻¹</td>
</tr>
</tbody>
</table>

Table 2. Impact of anaemia on oxygen delivery. Hb, haemoglobin; CaO₂, arterial blood oxygen content; DO₂, oxygen delivery to tissue; CO, cardiac output.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hb 15 g dl⁻¹</th>
<th>Hb 7.5 g dl⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspired oxygen (%)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Pao₂ (kPa)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sats (%)</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Dissolved oxygen (ml litre⁻¹)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hb-bound oxygen (ml litre⁻¹)</td>
<td>197</td>
<td>98</td>
</tr>
<tr>
<td>Total CaO₂ (ml litre⁻¹)</td>
<td>200</td>
<td>101</td>
</tr>
<tr>
<td>DO₂ if CO 5 litre min⁻¹ (ml min⁻¹)</td>
<td>1000</td>
<td>505</td>
</tr>
</tbody>
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Table 3. Causes of imbalance between oxygen supply and demand in the perioperative period.

- Reduced oxygen delivery
  - Reduction in CO due to hypovolaemia or cardiac depression by drugs, e.g. anaesthetic agents
  - Decrease in oxygen saturation due to atelectasis, postoperative pneumonia, thromboembolic event
  - Further reduction in haemoglobin as a consequence of surgical blood loss or inhibition of erythropoiesis by the altered cytokine milieu
  - Increased affinity of haemoglobin for oxygen due to the leftward shift in the ODC by hypothermia

- Increased oxygen requirements
  - Pain
  - Fever
  - Shivering
  - The stress response
Evaluation

The most common causes of anaemia during the preoperative period are chronic blood losses, nutritional deficiencies, and anaemia of chronic disease. The following stepwise diagnostic approach has recently been proposed. The first step is to assess the bone marrow response to anaemia by measuring the reticulocyte count. A low reticulocyte count indicates a poor bone marrow response, which will be further classified according to the mean corpuscular volume, as micro, normo, or macrocytic. The most common cause of microcytic anaemia is iron deficiency, a diagnosis confirmed by low ferritin level and low saturation of transferrin. β-Thalassemia should also be considered in at-risk groups. Causes of normocytic anaemia include kidney and liver disease, anaemia of chronic disease (usually characterized by a high ferritin level and inflammatory markers), dimorphic anaemia (combined iron and B12 or folate deficiencies), early iron and B12 deficiencies, acute blood losses, and myelodysplasia. Macrocytic anaemia is usually classified as megaloblastic or non-megaloblastic depending on whether or not megaloblasts are present on peripheral blood smear. Megaloblastic anaemia is caused by folate and B12 deficiency and also certain anti-convulsive agents and cytostatic medications. Non-megaloblastic macrocytic anaemia can be related to excessive alcohol intake and liver or thyroid diseases. A high reticulocyte count indicates regenerative anaemia, which can be seen either in blood loss when there is no associated iron deficiency or in haemolytic anaemia. High levels of lactate dehydrogenase, serum iron, and free plasma haemoglobin and low level of haptoglobin further confirm the diagnosis of haemolysis. Direct and indirect Coombs tests allow distinction between immune and non-immune haemolytic anaemia. A simple flowchart to guide the investigation of preoperative anaemia is proposed (Fig. 3). It should be emphasized that preoperative anaemia is commonly multifactorial and when interpretation of results is not straightforward, input of a haematologist should be sought.

Management

While transfusion of allogenic red blood cells is a rapid means of correcting anaemia, it is now established that transfusion itself is associated with increased perioperative mortality and morbidity. Iron deficiency anaemia: the priority in newly diagnosed iron deficiency anaemia is to rule out occult gastrointestinal blood loss. Iron can be replaced by the oral or parental route. Oral iron is prescribed as a 100–200 mg daily dose; its advantages include low cost and ease of administration but its bioavailability is limited and tolerance can be poor. I.V. iron is more effective, particularly when the interval to surgery is short but associated with a risk of anaphylaxis. Preparations with the best safety profile are ferric gluconate and iron sucrose. The total i.v. iron dose (TID) required can be estimated by the formula: TID (mg) = (Hbtarget – Hbcurrent) (g dL⁻¹) × weight (kg) × 2.4.

Vitamin deficiency anaemia: folate and vitamin B12 deficiencies alone seldom cause anaemia but should be corrected

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**Fig 3** Suggested algorithm for the aetiological diagnosis of preoperative anaemia. U&E, urea and electrolytes; LFTs, liver function tests; LDH, lactate dehydrogenase; AED, anti-epileptic drugs.
when identified in an anaemic patient. Folate deficiency is treated by administration of 1 mg oral folic acid per day. The treatment of vitamin B12 deficiency usually comprises daily i.m. injection of 1 mg of cobalamine for a week followed by a 1 mg injection monthly.

- Renal anaemia and anaemia of chronic disease: recombinant human erythropoietin (rHuEpo) is an established therapy for patients suffering from renal anaemia and anaemia related to chronic disease. Prescription should be directed by a nephrologist or haematologist, but administration is usually via subcutaneous injection three times per week. The use of rHuEpo requires simultaneous iron supplementation, preferably i.v., to provide sufficient iron to support the augmented erythropoiesis. Caution is advised in patients with a history of ischaemic heart disease or cancer as high doses of rHuEpo are associated with an increased risk of thrombotic events and tumour progression.

These approaches to correct anaemia before surgery reduce perioperative transfusion rates, postoperative infectious and ischaemic complications and length of hospital stay. Furthermore, they conserve blood stocks and are associated with cost savings.

Despite efforts to identify and correct preoperative anaemia, some patients will still present for surgery with low haemoglobin, particularly if they require urgent intervention. In these circumstances, steps should be taken to minimize blood loss, optimize tolerance to anaemia, and if necessary transfuse red cells. They should be monitored carefully for postoperative bleeding and complications such as ischaemia.

**Conclusions**

Preoperative anaemia is a significant but modifiable risk factor for adverse perioperative events. Widespread adoption of a structured approach to detection, evaluation, and management is recommended.

**Declaration of interest**

None declared.

**References**


Please see multiple choice questions 1–4.