Pre-optimization of the anaemic patient

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Abstract

Preoperative anaemia is common. Its prevalence varies according to the population studied and the definition of what constitutes anaemia. Where the widely accepted definition of the World Health Organization is used (haemoglobin concentration <130 g/l in men or <120 g/l in women), between 20% and 60% of surgical patients are found to be anaemic. Anaemia is well known to contribute to increased perioperative risk. In contrast to the other well-known risk determinants (e.g. age, magnitude of surgery, the presence or absence of a cancer diagnosis, renal failure etc.), anaemia is potentially modifiable. This article will give an overview of the approach to a patient found to be anaemic before surgery.

Keywords Blood; intravenous iron; iron-deficiency; preoperative anaemia; transfusion

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Learning objectives

After reading this article, you should be able to:

- understand why traditional patterns of care — ignoring the anaemia, or correcting the low Hb value by reflexively transfusing Hb — are suboptimal
- provide a framework for approaching the further work-up and simultaneous treatment of an anaemic patient in the pre-surgical setting

The myths of preoperative anaemia unravelled

Donated blood administration is a life-saving treatment in some conditions (e.g. exsanguination or bone marrow failure). Traditionally, allogeneic blood transfusion (ABT) has also been central to the management of preoperative anaemia. One concern is that, in patients who are anaemic preoperatively, surgical blood loss may precipitate dangerously severe acute anaemia and consequent tissue oxygen deficiency. For this reason, preoperative 'top-up' blood transfusions have traditionally been used to prepare anaemic patients for surgery, with transfusion often intended to restore a normal or near-normal Hb concentration before operation.[1]

The notion of ABT as an unequivocally positive treatment was challenged with publication of a series of randomized trials of 'restrictive' (typically 70–80 g/l depending on the population) versus 'liberal' (typically 90–120 g/l) transfusion thresholds. A restrictive approach was superior to liberal transfusion in critical illness and gastrointestinal haemorrhage, non-inferior after hip fracture repair, and 90 g/l was possibly superior to 75 g/l after cardiac surgery with bypass. None of the above trials are directly applicable to the preoperative patient. A recent systematic review, conducted during production of a national guideline,[1] found only one small randomized pilot study comparing preoperative transfusion for patients with mild anaemia with no transfusion. Surgical outcomes were no different and overall transfusion requirements were not reduced. Whatever the optimal threshold, the traditional practice of transfusion as treatment for anaemia (top-up to normal or near-normal values) is not evidence based.[1]

While the traditionally well-understood complications of ABT are rare (major morbidity around 1:20,000 transfusions, and death around 1:200,000 transfusions), it is also becoming clear that ABT carries other hazards. These include immunomodulation (cross-matched, donated blood is still foreign material), a higher incidence of infective complications (not transmitted via the donated blood), and increased rates of cancer recurrence.[1,2] Furthermore, conditions such as variant Creutzfeld–Jacob disease, HIV and hepatitis C were all transmitted via donated blood before it was appreciated that this was possible — at the time they were 'unknown unknowns'.[3]

The risks associated with untreated preoperative anaemia

Another traditional pattern of care is to proceed with planned surgery despite mild or moderate anaemia, accepting that severe perioperative or postoperative anaemia is likely to occur and that ABT may be required. In the anaemic patient undergoing surgery, ABT and/or acute-on-chronic anaemia are thus traditionally viewed as nearly inevitable.[3] Complications of ABT that are easily and directly attributable to the transfusion episode were seen as rare (though likewise near inevitable) and not the responsibility of the person prescribing the transfusion. On the other hand, decisions to withhold ABT or to use transfusion alternatives, were seen to bring responsibility for any adverse events that follow.[3]

Large observational studies have been conducted that evaluate the relationship between anaemia (whether treated by ABT or not) and surgical outcomes. These consistently show the following:

- Anaemic patients are at increased risk of major perioperative and postoperative complications, including death.
- Even mild anaemia (Hb >100 g/l) increases risk.
- Anaemic patients are more likely to require ABT, even where restrictive thresholds are used.

The above relationships persist despite sophisticated statistical analyses that control for other preoperative factors (e.g. age, renal function, smoking status, gender etc.).[1,2]

The benefits of management of preoperative anaemia

Randomized trials indicate that patients' transfusion risk may be reduced by preoperative treatment to increase red cell mass.[1]

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This is unsurprising, since the likelihood of transfusion has to vary as a function of:

- starting Hb
- Hb mass loss perioperatively
- Hb threshold for transfusion.

The randomized studies all tended to recruit a defined group of patients undergoing similar surgery with similar blood loss, and also standardized transfusion thresholds.

For some patients reducing the risk of transfusion is of itself a positive outcome (e.g. those who refuse blood for cultural/religious reasons, those with complex allo-immunization problems, or those concerned about the possible risks of ABT). National guidance on consent for transfusion is available, and is explicit that patients should be informed about transfusion alternatives and their right to refuse transfusion.[4] There is, however, only observational evidence that surgical outcomes are improved when anaemia is corrected before operation.[1] Improved outcomes in observational studies have included shorter length of stay, reduced re-admissions, fewer re-operations for infection and lower heathcare costs.

In addition to the benefits to the surgical patient (possible recipient), there is also a public health benefit from reducing the reliance we place on donated blood. The blood supply is by definition limited, the donor population is decreasing in numbers, and the supply chain is potentially vulnerable to natural disasters, infective pandemics and demographic change.[1] Furthermore, there are groups of patients for whom no alternative exists but to receive ABT, and anaemia treatment without blood conserves the scarce resource for them.

An evidence-based approach to the management of preoperative anaemia

Anaemia detected during surgical work-up is subtly different from anaemia diagnosed in other settings:

- Anaemia may be expected as consequence of the presenting surgical problem, may be incidental, or may be due to previously undetected disease that is more serious than the presenting problem (e.g. iron deficiency anaemia due to gastrointestinal cancer, detected during work-up for hip replacement).
- The anaemia is not the patient's presenting complaint; anaemia treatment should therefore not interfere with managing the primary problem whenever possible.
- Mild anaemia may be more important in the surgical context than is usually the case, for the reasons described above.
- The anaemia is likely to get worse as a consequence of the planned surgery — both because of Hb loss and because the inflammatory response to surgery changes bone marrow function (see below).
- Anaemia treatment is likely to be required for a shorter time period than in general haematology practice.

Causes of anaemia in the preoperative patient

Anaemia is not simply an abnormal laboratory value — it is rather a possible manifestation of a number of conditions, some serious. Diagnosing anaemia in the surgical setting is no different to diagnosis in general medical practice and the reader is referred to general medical textbooks for further reading.[5]

Practically speaking, the important diagnoses in the surgical setting are:

- Iron deficiency anaemia:
  - The serum ferritin concentration is the most sensitive marker of iron status in the absence of inflammation, with <30 mcg/l indicating iron deficiency.
  - The red cell indices (microcytosis and/or hypochromia) only change late in the disease process and are poorly sensitive.
  - Hypoferritinaemia (<15 mcg/l) without anaemia is also diagnostic of iron deficiency.
  - Iron deficiency anaemia is both the most common diagnosis world-wide, and the diagnosis most likely to be due to serious underlying disease (see below).
  - Iron deficiency is simple to treat, and patients' functional status consistently improves as a result.[1]
- Functional iron deficiency (FID):
  - FID is a condition where insufficient iron is available at bone marrow level, but iron is sequestrated in the reticulo-endothelial system and total body iron levels are normal or near normal.
  - It arises as consequence of chronic inflammation and increasing age, and is mediated by the action of the hepatic protein hepcidin.
  - In the presence of inflammation, serum ferritin is falsely elevated and values <100 mcg/l may still be consistent with FID.
  - Many patients with normochromic normocytic anaemia, who would have traditionally been termed as having 'anaemia of chronic disease' in fact have FID.
  - Options to confirm the diagnosis are serum transferrin saturation (<20%), bone marrow biopsy (invasive and only justified after haematology opinion) or a trial of parenteral iron, which is also the effective treatment.
- B12 and/or folate deficiency:
  - Though less common than iron deficiency, anaemia due to B12 or folate deficiency is easy and cheap to treat.[1]
  - As for iron deficiency, the red cell indices change relatively late in the disease course — serum levels are more sensitive.
- Anaemia due to other causes, e.g. renal failure or the inherited haemoglobinopathies (e.g. thalassaemia) are less amenable to treatment.

The importance of preoperative recognition of anaemia

Anaemia may be expected as part of the presenting complaint, (e.g. in patients who were referred for colorectal cancer surgery, or in women referred for procedures to treat menorrhagia). However, surgery is also a 'sentinel event' for many patients who have never before had cause to be investigated. Preoperative anaemia therefore may be divided into two groups:

- Those for whom the anaemia is benign of itself, but a modifiable risk factor for surgery.
- Those for whom the anaemia itself is serious or sinister.

The likelihood of previously undetected anaemia having a serious underlying cause varies as a function of the patient's demographics, and of the anaemia severity, with iron deficiency anaemia (IDA) being an additional risk.[1,6] Broadly speaking,

mild or moderately anaemic premenopausal women are low risk for serious underlying disease – the prevalence of a cancer diagnosis in this group being <1%.[1] On the other hand, IDA in men or post-menopausal women is associated with a >10% risk of cancer – this group should be considered for gastroenterology referral and elective non-cancer surgery should be postponed.[1,6]

Evidence-based treatment options

As described above, transfusion as first-line therapy for anaemia is not evidence-based. In certain circumstances (e.g. very severe or symptomatic anaemia) transfusion may be indicated even if no surgery was planned. Furthermore, in situations where an appropriately restrictive transfusion threshold is certain to be crossed (e.g. urgent major surgery in a severely anaemic patient) there is no evidence to suggest whether preoperative transfusion is better or worse than intra-operative transfusion.

There is also a recent vogue for 'scattergun treatment' of anaemia without transfusion – small trials have evaluated combined IV iron and erythropoietin regardless of the cause of anaemia. While effective at reducing transfusion risk, these treatments have not been shown to improve other outcomes and safety data are lacking. Such strategies are not currently recommended for routine use – anaemia treatment must be rational and based on assessment of the likely cause.[1]

Other treatments do have evidence in support:[1]

- Oral iron:
  - Iron tablets are cheap, effective when taken consistently, and very safe.
  - They are as effective as parenteral iron in the medium term (up to around 12 weeks) and the rate of Hb increase is typically around 10 g/l/week with optimal absorption.
  - After the anaemia recovers, treatment should continue for at least 3 months until iron stores are replete.
  - Oral iron is therefore the treatment of choice for patients whose surgery is not urgent.
  - Oral iron is unlikely to be effective in FID.[1]
- Intravenous iron:[1]
  - Some older IV iron preparations had problems related to high levels of circulating free iron during administration, with anaphylactoid reactions being relatively common.
  - Other older preparations therefore linked the iron to dextran chains, which decreased anaphylactoid reactions, but these may rarely cause anaphylaxis.
  - Newer preparations present the iron encased in a carbohydrate shell, with free iron only becoming available once the molecule is absorbed by macrophages. These preparations are safe, with a serious adverse event rate of <1:200,000.[1]
  - European Medicines Agency recommendations are that IV iron be administered in areas where resuscitation facilities are available.[1]
  - IV iron is more effective than oral iron in the short term, and speed of response is greater in more severe anaemia.
  - IV iron is therefore recommended in IDA or FID before expedited surgery.[1]
- Erythropoetin (EPO):
  - EPO has a large body of randomized literature in support, for reduction in transfusion risk only.
  - There is no randomized evidence that its use improves other patient outcomes, and the costs are higher than transfusion costs.
  - Its routine use should therefore be limited to situations where a clear indication exists for transfusion risk reduction per se.[1] Examples are patients who refuse transfusion (whether for religious reasons or not) or those with complex antibodies where blood is difficult to source.

Treatment algorithms for management

Although various algorithms have been published,[1] these are either speciality-specific (e.g. the Network for Advancement of Transfusion Alternatives algorithm for elective orthopaedic surgery) or institution-specific (e.g. the examples available via www.bcshguidelines.com). Each institution should design its own algorithms that integrate with local surgical pathways, so that anaemia management may be efficient and not disruptive to the management of patients' primary surgical problems. ◆

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