Anaesthesia 2019, 74 (Suppl. 1), 49–57 doi:10.1111/anae.14466

Review Article

Optimisation of pre-operative anaemia in patients before elective major surgery – why, who, when and how?

K. E. Munting[1] and **A. A. Klein**[2]

1 Consultant, Department of Anaesthesia, University Medical Centre Utrecht, The Netherlands
2 Consultant, Department of Anaesthesia and Intensive Care, Royal Papworth Hospital, Cambridge, UK

Summary

Anaemia in surgical patients is a common and serious problem; around 40% of patients presenting for major surgery are anaemic. Patients with pre-operative anaemia have significantly higher rates of morbidity and mortality and are likely to be transfused red cells. In addition, red cell transfusions are independently associated with worse outcomes. Pre-optimisation of anaemia in surgical patients leads to higher pre-operative haemoglobin concentrations and less need for transfusion. Patients undergoing major surgery (defined as blood loss > 500 ml expected or possible) should be optimised if their haemoglobin concentration is less than 130 $g.l^{-1}$ on screening. Detection of anaemia should follow listing for surgery as soon as possible to allow enough time for optimisation. The most common cause of pre-operative anaemia is iron deficiency, which can be treated with iron therapy. Iron clinics should be set up in either primary or secondary care to allow for optimal treatment. In this review, we present literature supporting the optimisation of pre-operative anaemia and propose a treatment algorithm.

Correspondence to: K. Munting
Email: k.e.munting@umcutrecht.nl
Accepted: 16 July 2018
Keywords: anaemia; pre-operative; transfusion; treatment

Introduction

The World Health Organization (WHO) states that every reasonable measure should be taken to optimise the surgical patient's own blood volume using a patient blood management (PBM) approach [1]. Multiple guidelines have been developed to support hospitals in the implementation of patient blood management, including the management and optimisation of pre-operative anaemia [2–6] and cell salvage [7]. Patient blood management has been shown to improve outcomes and reduce healthcare costs in a number of studies. In total knee and hip arthroplasty [8–10] and cardiac surgery [11], implementation of patient blood management has been shown to lead to a reduction in transfusion, hospital stay, morbidity and re-admission to hospital. One prospective multi-centre study evaluated the safety of a hospital-wide implementation of patient blood management; 54,513 patients before patient blood management implementation were compared with 75,206 patients after patient blood management implementation, and patient blood management was shown to be non-inferior. Furthermore, acute renal failure and transfusion were reduced, the mean (SD) number of units transfused per patient being reduced from 1.21 (0.05) to 1.00 (0.05), a 17% relative reduction in the number of units of red cells transfused, $p < 0.001$) [12]. A large Australian study provided data on the implementation of patient blood management in four tertiary hospitals in 605,046 patients. A 5-year programme of implementation was initiated and the final year was compared with the baseline year with regard to red cell transfusion, haemoglobin concentration on admission, mortality and costs. The number of red cell transfusions decreased by 41% (RR (95%CI) 0.59 (0.58–0.60); $p < 0.001$) and fewer elective surgical patients were anaemic on admission (20.8% vs. 14.4%, $p = 0.001$).

Mortality decreased, with the adjusted odds ratio (95%CI) for death being 0.72 (0.67–0.77), $p < 0.001$, and costs were reduced by an estimated 100 million Australian dollars over 5 years [13].

Surgical patients with anaemia are at increased risk for morbidity and mortality and are likely to be transfused with red cells [14–17]. Red cell transfusion itself also increases morbidity and mortality [16–18]. Therefore, detection and treatment of pre-operative anaemia as part of patient blood management is crucial. In this review we discuss the practical management of pre-operative anaemia in surgical patients, targeting those undergoing major surgery where more than 500 ml blood loss is expected [5].

Why?

A significant proportion of patients are anaemic pre-operatively. An average of 39.1% of major surgical patients have pre-operative anaemia [16], the pre-valence ranging between 20 and 45% depending on the type of major surgery [19]. An increasing body of evidence has shown increased morbidity and mortality in patients with anaemia in most surgical specialties. Musallam et al. studied the prevalence and outcomes of anaemia in the dataset of the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP), a prospective validated outcomes registry from 211 hospitals worldwide including a wide variety of major surgical disciplines. A total of 227,425 patients were included and an increased risk of 30-day mortality and morbidity was found in patients with anaemia compared with non-anaemic patients [14]. The European Surgical Outcomes Study (EuSOS) dataset of 46,539 patients showed similar results for patients with pre-operative anaemia who underwent major surgery. Patients with moderate or severe pre-operative anaemia had higher in-hospital mortality, prolonged hospital stay and more intensive care admissions [15]. A recent meta-analysis included 24 observational studies (949,445 patients) which compared outcomes after major surgery, including cardiac surgery, in patients with and without pre-operative anaemia. Patients with pre-operative anaemia were at increased risk of major adverse outcomes including mortality, the OR (95% CI) being 2.90 (2.30–3.68); acute kidney injury, 3.75 (2.95–4.76); and infection 1.93 (1.17–3.18) [16]. In addition, the severity of pre-operative anaemia has also been shown to affect outcome. In cardiac surgery, haemoglobin concentration is linked to increased risk for red cell transfusion and morbidity and mortality. Any haemoglobin < 130 g.l^{-1} is associated with worse outcomes, and a 10 g.l^{-1} decrease in haemoglobin is associated with a 43% (95%CI 40–46%) increased risk for red cell transfusion and a 16% (10–22%) increase in mortality [17].

In surgical patients, red cell transfusion is associated with an independent increase in worse outcomes. A large study used propensity matching within the dataset of the ACS NSQIP to compare the effect of red cell transfusion. Higher rates of morbidity and mortality were found in patients receiving one unit of red cells compared with patients who were not transfused [18].

At present, the evidence that active management of pre-operative anaemia reduces peri-operative morbidity and mortality is limited; however, a number of major randomised controlled trials (RCT) are in progress [20–24]. To date, no large high-quality trials have been published comparing treatment of pre-operative anaemia with standard care/placebo, leaving us with only indirect evidence. Many studies have shown an increase in haemoglobin and a decrease in red cell transfusion when iron deficiency anaemia is treated with iron therapy [2]; the effect on other patient outcomes is awaited.

Iron deficiency anaemia is the most common type of anaemia both worldwide [25] and in the surgical population [26]. In a study of 3342 patients (44.5% of whom were women) scheduled for orthopaedic surgery, cardiac surgery, colorectal cancer resection, radical prostatectomy and gynaecological surgery, 36% of patients were anaemic and of those 62% had absolute iron deficiency anaemia and 10% had anaemia with iron sequestration [27].

The National Institute for Health and Care Excellence (NICE) recently published standards which state that patients undergoing major surgery and who have pre-operative anaemia and iron deficiency should be offered iron therapy [2]. In the general population, evidence indicates a favourable effect of iron therapy in patients with iron deficiency anaemia without chronic kidney disease. The haemoglobin concentration increases in patients receiving either intravenous (i.v.) or oral iron (mean differences 3–30 g.l^{-1} i.v. and 3–31 g.l^{-1} oral respectively, both vs. inactive control) and fewer iron-treated patients receive red cell transfusion compared with inactive control [28]. The NICE guidelines on transfusion included five RCTs comparing i.v. iron with placebo [29–33] and two RCTs comparing oral iron with placebo [34, 35] in different types of surgery. Fewer anaemic patients were found to require red cell transfusion after treatment with iron [2]. Since then, more studies have been published supporting these conclusions [36–39]. No clear differences in other outcomes have been found so far. However, with the current evidence, a treatment impact of pre-operative

anaemia on clinical outcomes cannot be excluded and appropriate treatment of patients with pre-operative anaemia is indicated.

Who?

All patients for elective surgery in whom blood loss is expected to be > 500 ml should have their haemoglobin checked pre-operatively and be investigated if they are found to be anaemic. In the general population, anaemia is defined as a haemoglobin < 130 $g.l^{-1}$ in men and < 120 $g.l^{-1}$ in women by the WHO [40]. We have proposed that the cut-off value/trigger be changed to a haemoglobin > 130 $g.l^{-1}$ for both men and women. Women with haemoglobin levels between 120 and 129 $g.l^{-1}$ are not considered to be anaemic according to the WHO definition, leaving them at a potential disadvantage when undergoing major surgery [41]. These women will not undergo further investigation or treatment of their reduced haemoglobin, even though they are more likely to need peri-operative red cell transfusion due to their lower circulating volume, despite losing similar amounts of blood during surgery as men [42, 43]. A large multi-centre cardiac surgery study showed that, regardless of sex, lower haemoglobin was associated with increased transfusion requirements, prolonged hospital stay and higher mortality. Any reduction below 130 $g.l^{-1}$ was associated in a linear manner with worse outcomes [17]. Furthermore, women with haemoglobin levels between 120 and 129 $g.l^{-1}$ undergoing cardiac surgery are more likely to be transfused, and are transfused more units of red cells and stay longer in hospital [44]. Therefore, we propose a change in the trigger for the treatment of anaemia in women undergoing major surgery to haemoglobin < 130 $g.l^{-1}$ for both sexes [45].

Oncology

Red cell transfusion is associated with a negative impact on survival and tumour recurrence in patients undergoing oncological surgery. Cancer-related anaemia is common (39–54% of cancer patients) and is influenced by multiple factors; this includes a specific process in cancer-related anaemia which is a cytokine-mediated process leading to impaired iron utilisation through hepcidin upregulation, suppressed erythroid maturation and reduced erythropoietin production [46, 47]. Anaemia may shorten survival time in cancer patients [48] and worsen local tumour control [49]. In addition, meta-analyses in different types of cancer show that red cell transfusions increase the risk of tumour recurrence and decrease survival rates [50–56]. Pre-operative anaemia in patients for colorectal cancer surgery is common (30–67%) and is a cause for concern [49]. The mechanism for development of anaemia is often through ongoing tumour-induced blood loss and/or the mechanism mentioned above where increased cytokine activity induces decreased iron uptake and utilisation through hepcidin upregulation, also known as anaemia of chronic disease or anaemia of inflammation [57]. Anaemia also leads to tumour hypoxia in patients with cancer, which means that chemotherapy and radiotherapy have less impact, because oxygen is essential for the cytotoxic effects of these treatments [58–60]. A recent systematic review found that anaemic patients with rectal cancer have a worse overall survival and disease-free survival; results patients with colon cancer did not show worse overall for disease-free survival [52]. Transfusion of red cells is associated with increased all-cause mortality and cancer-related mortality [61] as well as increased recurrence of colorectal cancer [62]. Whether the relationship between anaemia, red cell transfusions and morbidity/mortality is the cause is unknown. Several studies investigating the effect of treatment of pre-operative anaemia have been published showing an increase in pre-operative haemoglobin after i.v. iron treatment [37, 63]. To date, no studies have been published investigating treatment of pre-operative anaemia on clinical outcomes in this group of patients.

Up to 50% of patients with gynaecological malignancies have anaemia. The most common causes in this patient group are: blood loss from the tumour; renal dysfunction secondary to platinum-based chemotherapy and marrow dysfunction from chemotherapy and/or radiotherapy [46]. Many patients have iron deficiency anaemia [64]. Several studies have shown that a preventive strategy of administering i.v. iron during chemotherapy increases haemoglobin concentration and reduces transfusion [65–67].

Orthopaedics

Orthopaedic surgery is one of the most appropriate clinical fields for optimisation of pre-operative anaemia [68]. Orthopaedic surgery is a field where blood loss is likely, especially during major joint replacements [42]. The prevalence of pre-operative anaemia is 15–40% [69]. An ageing population requires more hip and knee arthroplasties and even more revision procedures, which are accompanied by more blood loss and higher transfusion requirements [70]. The majority of surgery is elective and postponing surgery for optimisation of pre-operative anaemia is warranted. Several studies have shown improved haemoglobin and decreased need for red cell transfusions with treatment of pre-operative anaemia [38, 39, 71] and the implementation of a patient blood management programme [8, 9]. Therefore, patients

scheduled for major elective orthopaedic surgery should be optimised if they have pre-operative anaemia.

Cardiac surgery

Patients undergoing cardiac surgery are at particular risk of the consequences of pre-operative anaemia due to risk of peri-operative blood loss, their underlying cardiac condition and the haemodilution associated with cardio-pulmonary bypass. In the UK, 23–45% of cardiac surgical patients have pre-operative anaemia [17]. Pre-operative anaemia is associated with worse outcomes [17, 72–75] and haemoglobin concentration is also independently associated with an increased risk of transfusion and mortality [17]. Furthermore, red cell transfusion is independently associated with a worse outcome [76] and optimisation of pre-operative anaemia leads to higher haemoglobin [77]. Whether treatment leads to prevention of worse outcomes is uncertain at this point, but two large trials are underway [21, 22]. Until then, it seems reasonable to start treatment of pre-operative anaemia in the cardiac surgical population because the potential for improvement is large.

Obstetrics

Lastly, pregnant women are of particular interest because anaemia is highly prevalent and a surgical intervention with concomitant blood loss (caesarean section or postpartum haemorrhage) is likely to result in transfusion if the woman is anaemic [78]. During pregnancy, physiological changes lead to a greater increase in plasma volume relative to the increase in haemoglobin mass, leading to a lower haemoglobin concentration. The definition for anaemia in pregnant women therefore differs from non-pregnant women, being haemoglobin < 110 g.l^{-1}, haemoglobin < 105 g.l^{-1} during the second and third trimesters, respectively and < 100 g.l^{-1} postpartum. Up to 30–40% of pregnant women have iron deficiency anaemia. Iron deficiency anaemia is associated with maternal and fetal morbidity. Systems for rapid investigation and treatment of anaemia in pregnancy should be available. Initial treatment is usually oral iron supplements [79]. However, if anaemia persists and oral iron is ineffective or not tolerated, i.v. iron administration is indicated.

When?

Detection of pre-operative anaemia should be carried out as soon as possible, at least 14 days before elective surgery [80] and preferably more than 30 days before surgery [68]. Patients at risk for moderate-to-high blood loss (> 500 ml) and > 10% chance of receiving red cell transfusion should be included for investigation of anaemia [5]. Laboratory investigations for the detection and diagnosis of anaemia should be performed directly after the decision to perform surgery. These laboratory investigations can be carried out in primary care or in the surgical outpatient clinic. Waiting until the pre-operative assessment/clinic is too late and causes an unnecessary delay. If anaemia is detected and treated in primary care, good communication between the general practitioner and the surgical team is essential to facilitate a timely and efficient approach. In the UK, patients have a median (IQR) period of 43 (16–94) days between listing and elective procedure and a median of 21 (IQR 10–49) days between pre-operative assessment and surgery. Patients undergoing elective orthopaedic surgery have the longest wait before surgery, and patients undergoing colorectal surgery the shortest, with a median of 15 days. Only 4% of patients undergo their procedure before the initial planned date [81]. Postponement of major, non-urgent surgery should be considered to allow the diagnosis and treatment of pre-operative anaemia [5].

A quick way to screen for anaemia is to use point-of-care testing with haemoglobin evaluation [82]. If anaemia (haemoglobin < 130 g.l^{-1}) is suggested using point-of-care testing, laboratory testing should follow; further evaluation should include full blood count, serum ferritin, transferrin saturation, vitamin B_{12} and folate, a marker of inflammation (e.g. serum C-reactive protein) and a marker of renal function (e.g. serum creatinine) [5].

How?

Iron deficiency anaemia has a complex origin, including nutritional deficiency and chronic inflammatory state resulting in absolute iron deficiency, functional iron deficiency or iron sequestration [83]. Absolute iron deficiency is a state where iron stores are severely decreased, resulting in anaemia. Functional iron deficiency, on the other hand, refers to insufficient iron mobilisation despite normal or elevated iron stores. Inflammation plays an important role in iron sequestration, where upregulation of hepcidin causes inhibition of intestinal iron absorption and increases iron sequestration in liver and macrophages, also known as anaemia of chronic disease. In Fig. 1, we propose a treatment algorithm for different types of anaemia from diagnosis to surgery based on a recent international consensus statement [5].

Treatment of iron deficiency anaemia should be carried out with iron supplementation, and there is good evidence that this results in higher haemoglobin concentrations, lower transfusion rates and better quality of life [2, 28, 84, 85]. When the interval between investigation and surgery

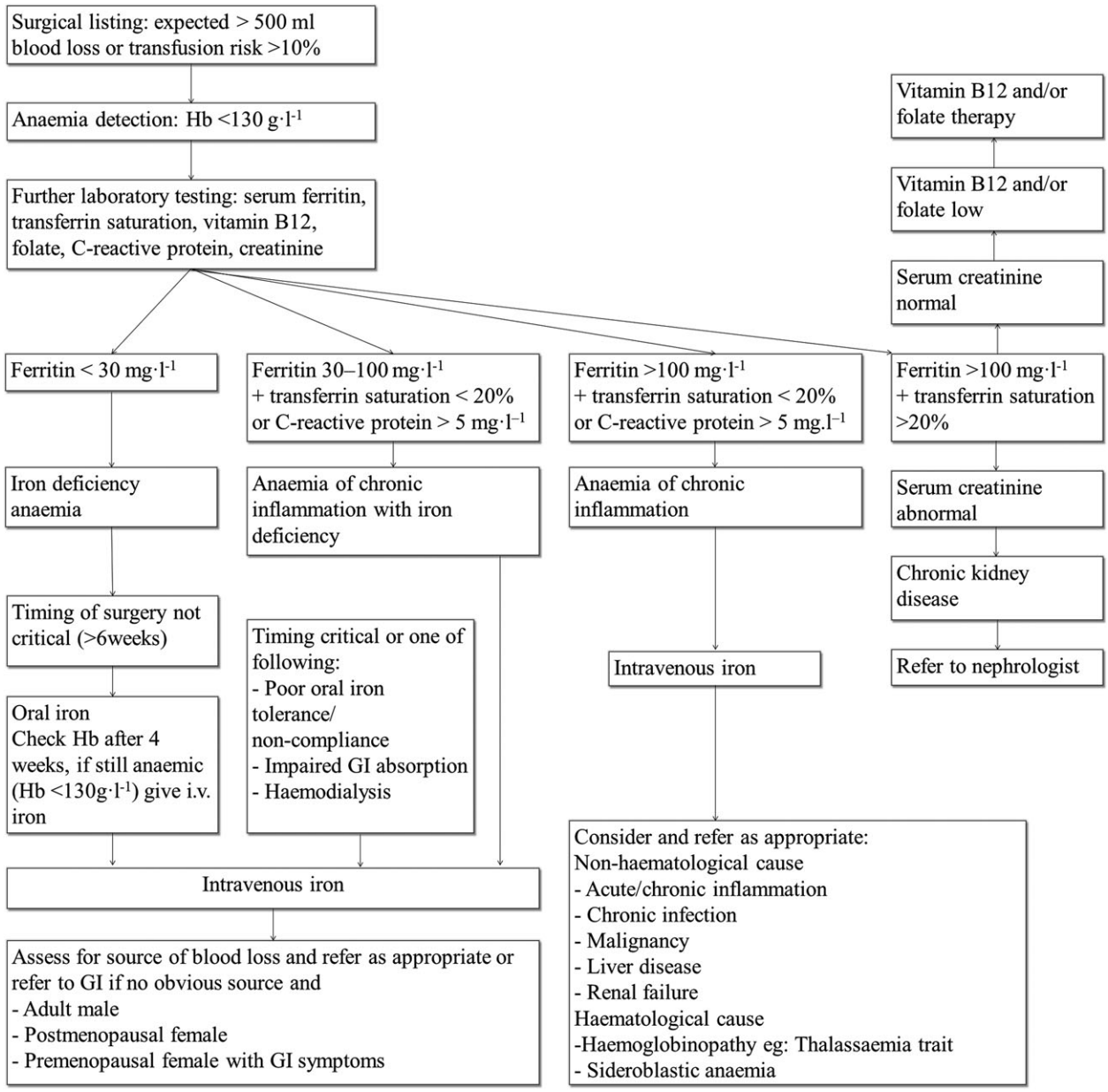

Figure 1 Treatment algorithm for pre-operative anaemia.

is sufficient (> 6 weeks), oral iron treatment may be considered [5]. Oral iron is cheap and both oral and i.v. iron increase haemoglobin concentration, whereas decreasing the need for red cell transfusion. Oral iron should be in the form of 40–60 mg elemental iron (one tablet or sachet) daily or 80–100 mg every other day [5]. A longer period of treatment is required for oral iron compared with i.v. iron and more side-effects occur [84]. Gastro-intestinal side-effects might lead to poor compliance with oral iron treatment. In practice, monitoring of efficacy for oral iron is recommended after 4 weeks of treatment. Intravenous iron is indicated if oral iron is poorly tolerated, is ineffective (no increase in haemoglobin after 4 weeks), if there is insufficient time until surgery (< 6 weeks), or in case of functional iron deficiency [2, 5, 86].

Intravenous iron is a relatively safe treatment [87, 88]. A large systematic review was published in 2015 reviewing 103 trials comparing i.v. iron with placebo, no iron, oral iron or intramuscular iron. The trials were searched for the outcome of severe adverse events, such as infections and infusion, cardiovascular, neurological, respiratory, gastro-intestinal, thromboembolic and constitutional severe reactions. A total of 10,390 out of 19,253 patients received i.v. iron treatment. There was no increased risk of severe

adverse effects with i.v. iron, the relative risk (95%CI) being 1.04 (0.93–1.17). The one concern that was identified was a possible association between i.v. iron and infection, with a relative risk (95%CI) of 2.47 (1.43–4.28). However, only one type of i.v. iron preparation (ferric gluconate) had a significant increased risk when analysed separately. No death or case of anaphylaxis was reported by any trial [87]. Anaphylaxis as a complication of i.v. iron therapy has only been reported in spontaneous postmarketing reports and the total number of life-threatening and fatal events reported is very low. Provided that adequate measures are taken, the benefits of i.v. iron significantly outweigh the risks [89].

Iron clinics may be set up either in primary or secondary care to provide i.v. iron for patients with pre-operative anaemia. However, patients need to be monitored (oxygen saturation, heart rate and non-invasive blood pressure) during iron infusion (which can normally be administered in 15–30 min) and for 30 min afterwards; resuscitation equipment and trained personnel should also be available. This often means a secondary care environment is chosen, as such monitoring facilities are not common in primary care in the UK. However, some primary care commissioners have set up local services, including a mobile i.v. iron service in Norfolk (http://www.norfolkcommunityhealthandcare.nhs.uk/The-care-we-offer/Service-search/intravenous-therapy.htm).

Routine use of erythropoietin is not recommended; it is not licensed for this indication in the UK. Although erythropoietin reduces the number of transfused patients, number of red cell transfusions, and the length of hospital stay, it potentially increases the risk of thrombosis and mortality [90]. The risks of erythropoietin therapy appear to outweigh the benefits, but erythropoietin should only be considered in patients with pre-operative anaemia who refuse red cell transfusions (Jehovah's Witnesses [91]) or if the appropriate blood type for transfusion is not available [2].

The efficacy and safety in diagnosing and treating pre-operative anaemia should be evaluated yearly by collecting and presenting appropriate data. We recommend the following data should be collected: proportion of patients having surgery with treatable anaemia uncorrected; proportion of patients having surgery with treatable anaemia corrected; transfusion rate for surgical patients (pre-operative, intra-operative, postoperative); cancellation rate (due to anaemia); i.v. iron infusion reactions; transfusion reactions; length of hospital stay; readmission rate within 30 days and patient experience.

The future

The increased risk of morbidity/mortality due to anaemia before major surgery is well established [14–16] and awareness for pre-operative anaemia has been created through guidelines underlining the importance of optimisation through patient blood management [2–6]. It seems rational to optimise haemoglobin concentration in patients with pre-operative anaemia before undergoing major surgery. There is good evidence that iron therapy in the pre-operative period increases haemoglobin concentration and reduces transfusion. However, to date, no definitive trials have been published that show an impact on morbidity and/or mortality. Despite this, many national bodies recommend active treatment of iron deficiency anaemia with iron, and it has been a NICE quality standard of care in the UK National Health Service since 2017 [80]. The outcomes of ongoing major randomised controlled trials are keenly awaited.

Acknowledgements

No external funding. AK or his employer has received educational grant funding, honoraria or assistance with travel from CSL Behring, Haemonetics, Pharmacosmos, Fisher and Paykel, Massimo and Vifor Pharma. AK is the Editor-in-Chief of *Anaesthesia*. No other conflicts of interest declared.

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