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Review Articles

REVIEW ARTICLES

'Fit to fly': overcoming barriers to preoperative haemoglobin optimization in surgical patients†

M. Muñoz[1,*], S. Gómez-Ramírez[3], S. Kozek-Langeneker[4], A. Shander[5], T. Richards[6], J. Pavía[2], H. Kehlet[7], A. G. Acheson[8], C. Evans[9], R. Raobaikady[10], M. Javidroozi[5] and M. Auerbach[11]

[1]Perioperative Transfusion Medicine, School of Medicine, [2]Department of Pharmacology, School of Medicine, University of Málaga, Málaga, Spain, [3]Internal Medicine, Xanit International Hospital, Benalmádena, Spain, [4]Anaesthesiology and Intensive Care, Evangelical Hospital, Vienna, Austria, [5]Anaesthesiology, Critical Care and Hyperbaric Medicine, Englewood Hospital and Medical Center, Englewood, NJ, USA, [6]Division of Surgery and Interventional Science, University College London, London, UK, [7]Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University and The Lundbeck Foundation Center for fast-track hip and knee arthroplasty, Copenhagen, Denmark, [8]Division of Gastrointestinal Surgery, Nottingham Digestive Disease Centre NIHR, Biomedical Research Unit, Queen's Medical Centre, Nottingham, UK, [9]Department of Anaesthesiology, Cardiff & Vale University Health Board, Cardiff, UK, [10]Department of Anaesthesiology, The Royal Marsden NHS Foundation Trust, London, UK, and [11]Department of Haematology-Oncology, School of Medicine Georgetown University, Washington, DC, USA

*Corresponding author. E-mail: mmunoz@uma.es

Abstract

In major surgery, the implementation of multidisciplinary, multimodal and individualized strategies, collectively termed Patient Blood Management, aims to identify modifiable risks and optimise patients' own physiology with the ultimate goal of improving outcomes. Among the various strategies utilized in Patient Blood Management, timely detection and management of preoperative anaemia is most important, as it is in itself a risk factor for worse clinical outcome, but also one of the strongest predisposing factors for perioperative allogeneic blood transfusion, which in turn increases postoperative morbidity, mortality and costs. However, preoperative anaemia is still frequently ignored, with indiscriminate allogeneic blood transfusion used as a 'quick fix'. Consistent with reported evidence from other medical specialties, this imprudent practice continues to be endorsed by non-evidence based misconceptions, which constitute serious barriers for a wider implementation of preoperative haemoglobin optimisation. We have reviewed a number of these misconceptions, which we unanimously consider should be promptly abandoned by health care providers and replaced by evidence-based strategies such as detection, diagnosis and proper treatment of preoperative anaemia. We believe that this approach to preoperative anaemia management may be a viable, cost-effective strategy that is beneficial both for patients, with improved clinical outcomes, and for health systems, with more efficient use of finite health care resources.

Key words: blood, erythrocytes; blood, transfusion; surgery, preoperative period

†This Article is accompanied by Editorial Aev099.

Editor's key points

- The authors review the impact and effect of surgery in the context of pre-existing anaemia.
- Via a presentation of the relevant evidence, they elucidate an argument for preoperative correction of anaemia.

Despite its known risk, blood loss in major surgical procedures - especially orthopaedic, cardiac, gynaecological, and cancer resection - is still considered as routine and an acceptable outcome in surgery. Left untreated, blood loss can result in a marked decrease in postoperative haemoglobin (Hb) concentrations. As a consequence, a significant proportion of patients receive allogeneic blood transfusion (ABT) for acute postoperative anaemia that could have been avoided.

Whilst perioperative anaemia is common, the need for liberal or prophylactic ABT has been questioned, with growing interest in strategies to reduce reliance on ABT as a solution for surgical anaemia. The rationale behind its liberal use is ABT increases the patients' Hb concentrations quickly and effectively, restoring oxygen delivery and providing a reserve should further bleeding occur. As this hypothesised benefit of ABT has not been unequivocally demonstrated,[1 2] with a few possible exceptions such as sepsis and acute coronary syndrome,[3 4] restrictive transfusion or no transfusion may result in better clinical outcomes.

Multidisciplinary, multimodal and individualized strategies, collectively termed Patient Blood Management (PBM), aim to identify modifiable risks and optimise patients own physiology with the ultimate goal of improving outcomes.[5 6] This new standard aims at timely application of evidence-based medical and surgical concepts designed to maintain Hb concentration, optimize haemostasis and minimize blood loss in an effort to improve patient outcome.[5 6] PBM draws on a number of key strategies, previously using the three pillar approach which has evolved into 4 quadrants, by relying on detection and treatment of perioperative anaemia, managing perioperative coagulopathy, using interdisciplinary blood conservation modalities, and making patient-centred decisions.[6] PBM has been endorsed by the World Health Assembly (WHA), requesting the World Health Organization (WHO) to provide its member states with training and support on the safe, rational use of ABT and transfusion alternatives.[7] Several countries are now establishing PBM programs for elective surgery.[5]

Although the suggested benefits of PBM for both patient and health care system appear to be common sense, implementation is not necessarily straightforward and there are a number of barriers needed to overcome. A PBM program takes planning and forethought unlike reflex ordering of one or two units of blood, regardless of need. This is not surprising, considering that the whole system of blood banking and donor blood procurement, processing and distribution has been in place for decades. The efficiency and success of blood transfusion services in delivering individually matched blood products in a safe and effective manner is an important aspect facilitating work within the system as opposed to making changes and adopting new alternatives.

As depicted in Figure 1, strong leadership is required to establish and run a PBM program. The coordinator must interact with medical staff as part of planning, implementation and audit of the PBM program, to gain commitment. One discipline cannot manage the paradigm shift alone, and consensus among disciplines on the bundle of diagnostic, therapeutic and logistic interventions is recommended. Supporting this contention is the consensus among ten disciplines in Austria on anaemia management within the PBM program.[8]

The PBM coordinator requires support from hospital administrators (facilitating organization), health authorities (reallocating funding and providing regulations) and medical societies (offering advice to health authorities and developing clinical guidelines). Continuing medical education should be offered to health professionals in order to refresh and update knowledge on different perioperative strategies within each pillar committing to the program.

Among the various strategies utilized in PBM, perhaps the most important is the timely detection and management of anaemia. As early as 1970, Lunn & Elwood described the association of preoperative anaemia with poorer outcomes.[9] This has been corroborated by a number of studies demonstrating a substantial postoperative morbidity and mortality increase as preoperative Hb concentration decreases in major surgery patients.[10–18]

However, preoperative anaemia is still frequently ignored, with indiscriminate ABT used as a 'quick fix'. Consistent with reported evidence from other medical specialties and our

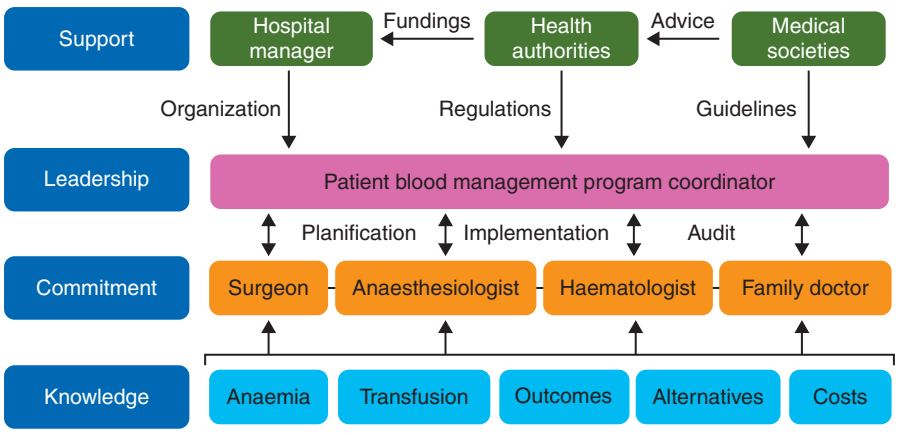

Fig 1 Requirements for implementing Patient Blood Management programs.

experience, this imprudent practice continues to be endorsed by non-evidence based misconceptions. After an informal meeting on PBM, held at London in March 2014, and attended by several of the authors (M.M., T.R., H.K., A.G.A,, C.E., R.R.B.), MM invited further authors to participate (J.P., S.G-R., S.K-L., A.S., M.J., M.A.), and drafted a preliminary list of misconceptions on perioperative anaemia (based on current practice of the authors, actively working in the field of perioperative anaemia, both in Europe and US). The preliminary list of misconceptions was circulated among the authors, and a selection was made, focusing on preoperative anaemia. It was agreed that misconceptions on postoperative anaemia deserved separate consideration. Later, M.M. wrote up of the first draft of the paper, which was circulated among authors. During several revisions, M.M. harmonized comments and contributions from the different authors to subsequent versions of the manuscript, until unanimous agreement on paper content was reached.

The authors are well aware of the guideline processes and systematic reviews, none of which have been able to move this forward. The intent of these authors is to use available and burgeoning data that 'disturb' the current *status quo* of ignoring this modifiable risk, which fosters barriers to a wider implementation of perioperative Hb optimization. Therefore, our goal is to provide a collective opinion with unanimous agreement against these misconceptions, and to highlight evidence-based alternatives associated with better outcomes. We would like to stress that this paper solely contains the authors' independent opinions. No pharmaceutical company has either funded or influenced the conception, development or writing of the manuscript.

Common misconceptions in the diagnosis and management of preoperative anaemia

Misconception 1: The prevalence of anaemia in surgical patients is similar to the general population

Using the WHO criteria to diagnose anaemia regardless of cause (Table 1),[19] global anaemia prevalence in 2010 was 32.9% (almost 2 billion people or 1 out of every 3 humans inhabiting the planet), with iron-deficiency anaemia (IDA) being the most common aetiology.[20] The prevalence of anaemia varies widely by geography, is higher in non-developed countries, age and gender.

In the USA, the Third National Health and Nutrition Examination Survey (NHANES III) study, conducted between1988–1994 in more than 26 000 individuals, reported an average prevalence of 6–8% in individuals up to age 74 years. In those older than 75, the prevalence of anaemia increased progressively with age, up to 23% in those more than 85.[21] This has been corroborated by a meta-analysis of 34 studies including 85,409 elderly individuals, in whom the overall prevalence among those in the community was 17%, increasing up to 40% in those hospitalized or in nursing homes. The prevalence fell to 6% when an Hb threshold of ≤11 g dl^{-1} was used, indicating anaemia was mild in the majority of patients.[22]

In patients undergoing major surgery, the prevalence of preoperative anaemia can reach up to 75%, depending on comorbidity, gender, age, and underlying pathology necessitating surgery.[15 23]

Table 1 Haemoglobin concentrations to diagnose anaemia at sea level*. * Haemoglobin in grams per decilitre; ** 'Mild' is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent (Adapted from[19])

Population	Non -Anaemia*	Mild**	Anaemia Moderate	Severe
Children 6–59 months of age	≥11	10–10.9	7–9.9	<7
Children 5–11 years of age	≥11.5	11–11.4	8–10.9	<8
Children 12–14 years of age	≥12	11–11.9	8–10.9	<8
Non-pregnant women (15 years of age and above)	≥12	11–11.9	8–10.9	<8
Pregnant women	≥11	10–10.9	7–9.9	<7
Men (15 years of age and above)	≥13	11–12.9	8–10.9	<8

Key point

According to the WHO definitions of anaemia, the likelihood of preoperative anaemia in the surgical population in developed countries can exceed the prevalence among the general population.

Misconception 2: The WHO definitions of anaemia are always valid for patients undergoing major surgery

According to the WHO, anaemia in adults is defined by an Hb <13 g dl^{-1} in men, and <12 g dl^{-1} in women, at sea level.[19] This definition is more a derivative of normal distribution of Hb concentrations and observed standard deviations from 'average', which is assumed to be the same as 'normal'. The higher prevalence of anaemia in women is expected to lower average observed Hb concentrations, resulting in acceptance of lower Hb concentrations in women as 'normal'.[24] While widely quoted and accepted, and also adopted by most blood conservation guidelines,[9 25 26] should a different definition in surgical patients be considered?

Females have lower circulating blood volumes than males. However, the same procedures performed in either gender often result in comparable amounts of blood loss. Therefore, when measured as a percentage of circulating blood volume, blood losses are higher in women and may result in higher transfusion rates. Although not confirmed by RCTs, data from the first Austrian benchmark study in orthopaedic and cardiac surgery (Fig. 2A), and from the OSTHEO study in orthopaedic surgery (Fig. 2B) corroborate these observations.[27 28] For a given preoperative Hb concentration (13 g dl^{-1}), the probability of ABT after lower limb arthroplasty was higher in females than in males (34 vs. 22%; Fig. 2B).[28] Moreover, in females, this probability was 40% for Hb 12 g dl^{-1}, decreasing to 24% for Hb 14 g dl^{-1} (Fig. 2B).[28] These data suggest that the 'conventional' definition of anaemia may not be reliable for classification of female surgical patients.

Key point

We believe the current definition of anaemia may not be reliable for the surgical population. For surgical patients, we propose redefining 'preoperative anaemia' and introducing the concept of 'sub-optimal preoperative Hb concentration' would make more sense. While waiting for more physiologically-sensible definitions, patients presenting with preoperative Hb <13 g dl^{-1} irrespective of gender should be considered anaemic. Therefore, we deem a desirable target for preoperative Hb optimization is

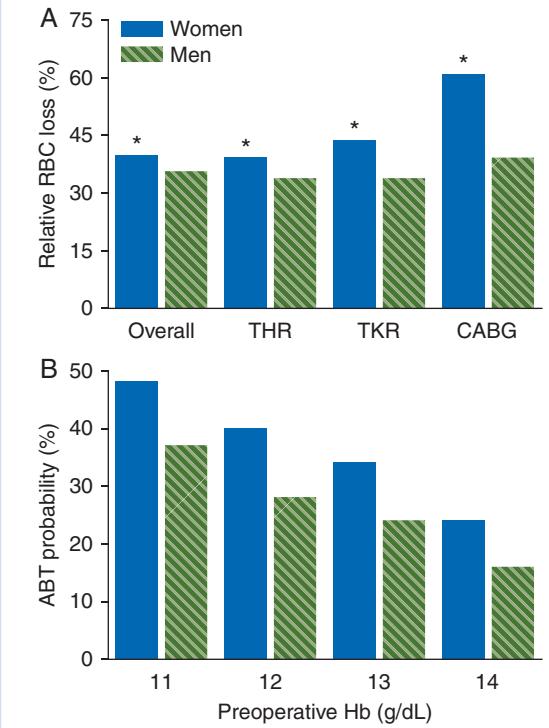

Fig 2 Relative RBC loss according to gender and surgical procedure (A), and ABT probability in lower limb arthroplasty, according to gender and preoperative haemoglobin concentration (B). THR, Total hip replacement; TKR, total knee replacement; CABG, coronary artery bypass grafting; Hb, haemoglobin; ABT, allogeneic blood transfusion. *P<0.001. (Data from ref. 27 and 28; see ref. 27 for details on relative RBC loss calculation).

a concentration ≥13 g dl^{-1} to minimise risk of unfavourable outcomes and ABT.

Misconception 3: preoperative anaemia may be caused by many conditions and some may be ameliorated or cured by the proposed surgery

The surgical population is becoming progressively older, and may present with a variety of co-morbidities, such as hypertension, hyperlipidaemia, diabetes, renal disease and inflammatory disorders, and nutritional deficiencies which can also cause anaemia. Unless nutritional deficiencies have been excluded, preoperative anaemia, even if mild, should be considered secondary to other conditions, and not necessarily directly associated with the one for which the surgery is being performed. One instructive case is a patient with rheumatoid arthritis or Crohn's disease who requires a total knee replacement.

It should be pointed out that even if a patient undergoing surgery for the same condition which caused anaemia, such as colorectal cancer, surgical intervention (resection of the tumour) is not likely to result in a fast, complete reversal.

Key point

Should the cause of preoperative anaemia be unrelated to the condition for which surgery is required, most probably it will not resolve after surgery. Therefore, we propose that preoperative anaemia requires full investigation as to the cause and appropriate treatment.

Misconception 4: preoperative anaemia poses no risk to patients, and scheduled procedures should not be delayed because of its presence

The association between preoperative anaemia and poor outcome has been described for many years. Several large observational studies in a variety of surgical settings confirmed an association between preoperative anaemia and worse postoperative outcomes.[10–18] While some have suggested that preoperative Hb concentration just reflects the severity of the underlying condition necessitating surgery, published evidence suggests it is an independent risk factor.[16 17] More often than not, after adjusting for confounding variables, the negative effects of preoperative anaemia persisted, independently of the underlying condition, in some patients even mild anaemia.[13 14 17 18] Preoperative anaemia is one of the strongest predictors for perioperative ABT, which is also associated with increased rates of postoperativemorbidity and mortality.[16] In the first Austrian benchmark study the incidence of preoperative anaemia in transfused patients was on average three times higher than in patients who did not receive transfusions (THA 28.6 *vs* 6.7%, TKA 29.9 *vs* 9.3%, CABG 33.1 *vs* 12.6%).[27] This was corroborated by the second Austrian benchmark study, which reported preoperative anaemia was not treated in 97 and 99% of anaemic orthopaedic and CABG patients, respectively.[29]

Therefore, we suggest unexpected preoperative anaemia (or suboptimal Hb concentration) should be considered an indication for rescheduling any elective major surgical procedure (moderate-to-high blood loss) until evaluation and treatment are completed, when possible.[30] However, minor procedures (no blood loss) can be performed while the anaemia evaluation is ongoing.

Key point

Preoperative anaemia is independently associated with worse clinical outcome, and whenever feasible should be corrected before the schedule procedure. This would require rescheduling major surgical procedures, when possible. Whether correction of preoperative anaemia can completely offset the excess of risk for postoperative complications, other than those associated with ABT, is presently unknown.

Misconception 5: preoperative anaemia management negatively impacts hospital personnel work-load and is not cost-effective

Recent guidelines recommend patients undergoing major surgery should have a complete blood cell count (CBC; including a reticulocyte count), iron status (serum iron, ferritin, and transferrin saturation) and a marker of inflammation tested, preferably 30 days before the scheduled surgical procedure.[9 25 30 31 32] For patients >65 years old, vitamin B_{12} and folic acid concentrations should also be determined.[30 31 33]

Standard laboratory tests requested for major elective surgical procedures usually encompass complete blood counts, coagulation screening, urea, creatinine, and electrolytes (Na^+, K^+, Cl^-). Adding additional, low-cost and widely available laboratory parameters, which are measured via automated laboratory work stations and using the same blood samples, will neither significantly increase laboratory personnel work-load nor patient inconvenience. Asking for 'additional tests for anaemia differential diagnosis' can be perceived as a discrepancy, with the global reduction of preoperative testing recommended by various guidelines.[9 25 32] Preoperative testing should not be misunderstood as an overall screening, but as focused risk stratification.

Preoperative anaemia is a risk factor; so for adequate risk-stratification and risk reduction, additional algorithm-based sequential testing is required in patients undergoing major surgical procedures, when considerable blood loss is anticipated. Figure 3 depicted an example for an easy-to-follow algorithm for laboratory tests.[34] Used in combination with clinical data, it allows for detection and classification of anaemia in surgical patients. At the preoperative assessment, the anaesthesiologist can inform patients individually and implement the appropriate therapy for anaemia correction; additional web-based information can be supplied to patients (e.g. www.oegari.at/patientenforum). Using this approach, haematinic nutrient deficiencies in non-anaemic patients can also be detected and treated.

There is enough evidence to support the cost effectiveness of pharmacological treatment of preoperative anaemia compared with ABT.[35 36] Another common misconception is to consider that ABT is free of charge. The costs for processing, screening, conservation, distribution and administration of packed red blood cells (PRBC) are high. A systematic review of the literature estimated that cost of a 2- PRBC unit transfusion in Western Europe is around € 800, but higher costs have been reported.[37 38] Moreover, irrespective of the preparative procedure, ABT is associated with several acute and delayed adverse side effects, some of which can be life-threatening. Should the indirect costs for detecting and correcting transfusion-related morbidity and compensation for harm be added, the real cost of ABT would be even higher.

Nutrient deficiencies without anaemia should also be corrected.[30] Non-anaemic patients with low ferritin concentrations (<100 ng ml^{-1}) undergoing surgical procedures with moderate-to--high blood losses may benefit from preoperative iron administration, as there may not be enough stored iron to replenish perioperative Hb loss and maintain normal iron stores.[33] An association between low preoperative ferritin concentrations, even without anaemia, and increased rates of nosocomial infections has also been observed.[39 40] To simplify care, 1 mg vitamin B_{12} (intramuscularly or subcutaneously) plus 5 mg/day oral folic acid can be administered to cover any possible deficiency.[41]

Key point

In most patients, detection and classification of preoperative anaemia (or suboptimal Hb concentration) before major surgical procedures can be accomplished using routine laboratory parameters, without significantly increasing health care professional work-load or hospital budgets.

Misconception 6: given that functional or absolute iron deficiency is the most common cause of preoperative anaemia (or suboptimal haemoglobin concentration), high-dose, oral iron supplementation is usually efficacious

Patients with iron deficiency anaemia (IDA) may benefit from oral iron therapy provided that: 1) a minimum period of 4–6 weeks is available before surgery, 2) there is tolerance of and no contraindications to oral iron, 3) significant doses can be administered, and 4) there is no active bleeding or inflammatory condition present.

In patients undergoing elective orthopaedic or colorectal cancer surgery, while some studies showed that preoperative oral iron (100–200 mg d^{-1}; 2–6 weeks) improved Hb concentrations, reduced transfusion rates and, in some patients, the length of hospital stay, others did not.[30]

Key point

Though IDA is a common cause of preoperative anaemia, anaemia of chronic inflammation (ACI) with or without ID is also frequent, because of patient's older age, co-morbidity and surgery-induced inflammation. The pathophysiology underlying ACI (inhibition of iron absorption and reduction of iron mobilization) and issues related to tolerance can explain the lack of efficacy of oral iron salts.[34]

Misconception 7: i.v. iron is hazardous and should only be used for treating severe preoperative anaemia

In both elective and non-elective surgery patients presenting with ID and suboptimal Hb, i.v. iron administration, with or

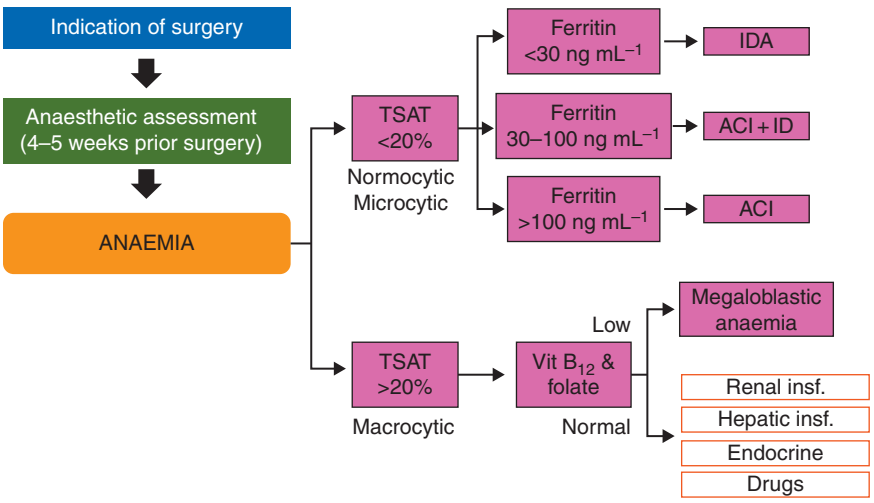

Fig 3 Example of an algorithm for anaemia classification in major surgery patients. IDA: Iron deficiency anaemia; ACI: Anaemia of chronic inflammation; ID: Iron deficiency; TSAT: transferrin saturation.

without recombinant human erythropoietin (rHuEPO), improves Hb concentrations, rapidly replenishes iron stores, and substantially cuts costs by decreasing ABT and ABT-related complications.[41–48] In the litany of published studies examining the role of i.v. iron to prevent surgery related ABT, serious adverse events (SAEs) have not been described,[41–48] though the number of surgical patients enrolled is insufficient to draw definitive conclusions concerning severe anaphylactic-type reactions attributable to i.v. iron, because of their very rare occurrence.

Two recent consensus statements recommend routine preoperative anaemia management.[30 31] However, i.v. iron administration in this population is not standard. One barrier to its use has been safety concerns, fuelled by misinterpretation of the incidence and clinical nature of SAEs, especially anaphylaxis and infection.[49] Early formulations of high molecular weight iron dextran were associated with rare occurrences of anaphylaxis and death. The formulations available in Europe, low molecular weight iron dextran, iron sucrose, iron isomaltoside and ferric carboxymaltose are much safer, with estimated SAE rates of <1:200.000 administrations, which is less than for ABT.[50 51] Nevertheless, i.v. iron is underutilized in a host of clinical settings where benefit has been demonstrated. Further supporting its use in the perioperative setting, i.v. iron was not associated with an increase in infection rate in a large series of cardiac surgery, elective lower limb arthroplasty or hip fracture patients, using established infection criteria.[46 52] Further adequately powered, prospective efficacy and safety trials in various surgical settings, that traditionally require ABT, would be required to reach evidenced-based conclusions.

In 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that: (1) i.v. iron preparations are used when iron supplements given by mouth cannot be used or have failed, especially in patients receiving dialysis for kidney failure, before and after operations, or in case of absorption disorders (2) The benefits of i.v. iron exceed risks, provided that adequate measures are taken to minimize the risk of allergic reactions; (3) Data on the risk of infrequent hypersensitivity comes largely from post-marketing spontaneous reporting and cannot be used to detect relative differences in the safety profile of different i.v. iron formulations.[53]

While some concerns may exist about i.v. iron's negative impact on bacterial infection and iron overload, it should be remembered that ABT delivers iron in addition to Hb. Each unit of RBC contains on average 200 mg of Fe and, in contrast to commercially available iron, this is Heme Fe which supports bacterial growth more readily.[54]

Key point

The use of i.v. iron allows for a rapid and more complete haematological response and replenishment of iron stores. With the exception of high molecular weight iron dextran which is no longer available, existing data strongly suggest all i.v. iron formulations have a favourable benefit-risk profile in the treatment of iron-deficiency anaemia in different acute and chronic conditions, when used appropriately.[53]

Misconception 8: newer i.v. iron formulations are very expensive and not cost-effective

The acquisition costs of low molecular weight iron dextran, iron isomaltoside-1000 and ferric carboxymaltose are considerably higher than that of iron sucrose or iron gluconate. However, these newer i.v. iron formulations allow the rapid administration of large single doses (≥1000 mg), facilitating a prompt and accurate preoperative iron replacement, with fewer visits necessary. These advantages may clearly out-weigh their higher acquisition costs, suggesting that novel i.v. iron formulations are a valuable tool for efficient and cost-effective treatment of iron deficiency in various therapeutic areas, including surgery.[35 55 56] A specific issue could be in which 'box' these medications are listed. If not in a green box, with compensation by the insurance or directly provided by the national health system, then it could be recommended to the national authorities to adjust access to this effective i.v. iron formulation.

Key point

The use of newer i.v. iron formulations for treating preoperative anaemia is safe, cost-effective and more efficient than oral treatment. In addition, newer i.v. iron formulations are more convenient both for the patient with fewer venopunctures, less time out from work, and for the health system with fewer visits to day hospital and ambulance transfers.

Misconception 9: preoperative erythropoietin administration poses a high thrombotic risk and should not be used

In Europe, recombinant human erythropoietin administration is approved for reducing ABT rate in patients with Hb between 10 and 13 g dl^{-1} and adequate iron stores, who are undergoing elective orthopaedic surgery and expected to have moderate blood loss.[31 32] In the US, this indication of rHuEPO is extended to other elective, noncardiac, nonvascular surgeries.[57] The recommended dose of rHuEPO is 300 U kg^{-1} day^{-1} subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery. An alternate dose schedule is 600 U kg^{-1} rHuEPO subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery. The minimum effective dose of rHuEPO in orthopaedic surgery is unknown, and a number of studies reported that one or two 40 000 IU rHuEPO doses are sufficient to reach the target Hb concentration (≥13 g dl^{-1}), especially when i.v. iron is co-administered.[41 45 46 58 59] Off-label use of rHuEPO has been suggested before cardiac surgery or gastrointestinal cancer resection.[30] Although 3 large RCTs demonstrated efficacy in significantly increasing Hb,[60–62] mortality end points were not reached in the third study.[62] Current recommendations do not include critically ill patients who do not have a previous indication for rHuEPO.[31]

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued alerts on the association between the use of rHuEPO and an increased risk of thromboembolic events, based on data from patients undergoing orthopaedic surgery without thromboembolic prophylaxis.[63] However, a recent meta-analysis confirms the efficacy of rHuEPO to reduce ABT rate, without observed difference in the risk of thromboembolism with respect to placebo, as the majority of patients received thromboprophylaxis and had low cardiovascular and thromboembolic risk.[64] In contrast, it is well established that ABTs are thrombogenic in surgical patients.[65]

When using rHuEPO for treatment of preoperative anaemia, a number of factors may help to reduce the risk of thrombotic events: (1) the duration of treatment is relatively short (3–4 weeks); (2) the majority obtain increased Hb concentrations for fewer than 15 days, as perioperative bleeding usually reduces Hb concentrations to values close to or less than 10 g dl^{-1}; (3) most receive adjusted doses of rHuEPO; and (4) co-administration of i.v. iron enhances the response to rHuEPO allowing dose reduction and reduction of platelet counts diminishing thrombotic risk.[66]

Key point

Within the approved indications, rHuEPO could be used to stimulate erythropoiesis in surgical patients. To safeguard the efficacy and safety of rHuEPO therapy, we advise an individually tailored dose, the presence of adequate iron ensured by the administration of adjuvant i.v. iron, and the deep venous thrombosis prophylaxis administered following existing guidelines.

Misconception 10: should other transfusion alternatives be implemented, preoperative anaemia management is not needed or is not a priority

It is well known that up to 40–50% of all ABT units are used in the surgical setting.[67] There is also a large inter-centre variability in the percentage of patients who receive ABT when undergoing a particular surgical procedure.[27 29] In order to reduce variability in transfusion practice, recent evidence-based guidelines recommend a 'restrictive' use of ABT when pharmacological options are not available or cannot be implemented.[31 32 68] The implementation of transfusion indicators has been shown to reduce variability in ABT practice, rate, volume, and associated complications, most noteworthy nosocomial infection and thromboembolic events.[69–71] However, in critically ill and surgical patients, it has been recently shown that transfusion of even a single unit of packed RBC increased the risk of postoperative complications and mortality compared with propensity-matched patients who did not received ABT.[72 73] There is also a recent publication suggesting a relationship between ABT and recurrence of colorectal cancer after potentially curative surgery.[74] Therefore, though it is one of the principles of PBM, the sole application of restrictive transfusion criteria is not enough, and additional blood conservation strategies should be implemented. Reduction of perioperative blood loss decreases exposure to ABT. It may be achieved through proper management of antiplatelet agents and anticoagulation therapy, maintenance of normothermia, use of controlled, induced or permissive hypotension, meticulous surgical haemostasis and, where possible, performing minimally invasive surgery.[31 32] Goal-directed and timely administration of drugs that inhibit clot lyses (e.g. antifibrinolytic agents), ensure clot strength and stability (e.g. fibrinogen concentrate,

Table 2 Summary of misconceptions and panel opinions (key points) regarding preoperative anaemia. ACI, anaemia of chronic inflammation; Hb, haemoglobin; IDA, iron deficiency anaemia; ID, iron deficiency; rHuEPO, recombinant human erythropoietin; WHO, World Health Organization

Misconception	Key points
The prevalence of anaemia in surgical patients is similar to the general population	The likelihood of preoperative anaemia in the surgical population in developed countries can exceed the prevalence among the general population.
The WHO definitions of anaemia are always valid for patients undergoing major surgery.	The concept of 'sub-optimal preoperative Hb concentration' (Hb < 13 g dl^{-1} for both genders) would make more sense. We propose a desirable target for preoperative Hb optimization is a concentration ≥13 g dl^{-1}.
Preoperative anaemia may be caused by many conditions and some may be ameliorated or cured by the proposed surgery	Should the cause of preoperative anaemia be unrelated to the condition for which surgery is required, most probably it will not resolve after surgery.
Preoperative anaemia poses no risk to patients, and scheduled procedures should not be delayed because of its presence.	Preoperative anaemia is independently associated with worse clinical outcome. Appropriate evaluation and treatment may require rescheduling the procedure, when possible.
Preoperative anaemia management negatively impacts hospital personnel work-load and is not cost-effective	In most patients, detection and classification of preoperative anaemia can be accomplished using routine laboratory parameters, without significantly increasing health care professional work-load or hospital budgets.
High-dose, oral iron supplementation is usually efficacious in correcting preoperative anaemia.	Both IDA and ACI with or without ID are frequent among surgical patients. Pathophysiology of ACI and issues related to tolerance can explain the lack of efficacy of oral iron salts.
i.v. iron is hazardous and should only be used for treating severe preoperative anaemia	i.v. iron allows for a rapid and more complete haematological response and replenishment of iron stores. Available data strongly suggest all i.v. iron formulations have a favourable benefit-risk profile, when used appropriately.
Newer i.v. iron formulations are very expensive and not cost-effective	Newer i.v. iron formulations are safe, cost-effective and more efficient than oral treatment. They also are more convenient both for the patient and for the health system.
Preoperative erythropoietin administration poses a high thrombotic risk and should not be used.	To safeguard the efficacy and safety of rHuEPO therapy, within the approved indications, we advise on an individually tailored dose, adequate iron ensured with adjuvant i.v. iron, and the deep venous thrombosis prophylaxis administered.
Should other transfusion alternatives be implemented, preoperative anaemia management is not needed or is not a priority	Implementation of different blood saving strategies does not preclude an adequate management of perioperative anaemia. The benefits of a PBM program would be greater whenever it includes patient's Hb optimization.

factor XIII concentrate), or promote clot formation (e.g. prothrombin complex concentrate), and perioperative red cell salvage, may contribute substantially to decrease the need for ABT and improve clinical outcome.[31 32]

Despite this, non-individualized, non-algorithm-based use of tranexamic acid and cell salvage is still common clinical practice and, even when used in combination with a restrictive transfusion protocol, these strategies may not confer total protection against the risk of ABT.[75 76] Nevertheless, in two large series of orthopaedic surgical patients, the beneficial effects of antifibrinolytic agents and perioperative cell salvage were significantly reduced in patients presenting with preoperative Hb <13 g dl^{-1}, and a significant proportion still received ABT.[77 78] Therefore, it is important to make clear, that there should not be an OR conjunction between the different pillars of a PBM program, but rather an AND conjunction; effecting an individualised, dynamic, multi-modal, and multi-disciplinary strategy resulting in improved patient outcomes.

Key point

Implementation of different blood saving strategies does not preclude an adequate management of perioperative anaemia. The benefits of a PBM program would be greater whenever it includes patient's Hb optimization.

Conclusions

We have reviewed a number of common unsubstantiated misconceptions regarding preoperative anaemia management, which constitute serious barriers for a wider implementation of preoperative Hb optimisation. In our opinion, these misconceptions should be promptly abandoned by health care providers and replaced by evidence-based strategies such as those advocated by PBM (Table 2). Preoperative anaemia is in itself a risk factor for worse clinical outcome, but also one of the strongest predisposing factors for perioperative ABT, which in turn increases postoperative morbidity, mortality and costs. Thus, detection, diagnosis and proper treatment of anaemia is central to the concept of PBM. In addition, it may be a viable, cost-effective strategy that is beneficial both for patients, with improved clinical outcomes, and for health systems, with more efficient use of finite health care resources, and therefore, should always be implemented.

Authors' contributions

M.M. contributed to the paper design, writing up of the first draft of the paper and harmonizing comments and contributions from the different co-authors in the subsequent versions of the manuscript. S.G-R., S.K-L., A.S., T.R., J.P., H.K., A.G.A., C.E., R.R.B., and M.J.: actively contributed to paper content and discussion. M.A. contributed to paper content and discussion, and editing the final version of the manuscript. All of the co-authors read and approved the final version of the manuscript.

Declaration of interest

M.M. has received industry-supplied funding for consultancies, lectures and travel from Pharmacosmos (Denmark) and Vifor Pharma (Spain), but not for this work, and is member of the editorial board of Revista Española de Anestesiología y Reanimación and Blood Transfusion. M.J. has worked as a contractor for the Society for Advancement of Blood Management and Gauss Surgical, and received consultancy fees from Gauss Surgical. No interest is declared by the remaining authors.

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