Anaemia in the older surgical patient: a review of prevalence, causes, implications and management

Judith Partridge[1,2] • Danielle Harari[1,2] • Jessica Gossage[3] • Jugdeep Dhesi[2]

[1]Kings College London, London SW1 3QD, UK; [2]Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK; [3]Lewisham Hospital, London SE13 6LH, UK

Correspondence to: Judith Partridge. Email: judith.partridge@gstt.nhs.uk

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Summary

This review provides the clinician with a summary of the causes, implications and potential treatments for the management of anaemia in the older surgical patient. The prevalence of anaemia increases with age and is frequently identified in older surgical patients. Anaemia is associated with increased postoperative morbidity and mortality. Allogenic blood transfusion is commonly used to treat anaemia but involves inherent risks and may worsen outcomes. Various strategies for the correction of pre- and postoperative anaemia have evolved. These include correction of nutritional deficiencies and the use of intravenous iron and erythropoesis stimulating therapy. Clear differences exist between the elective and emergency surgical populations and the translation of research findings into these individual clinical settings requires more work. This should lead to a standardized approach to the management of this frequently encountered clinical scenario.

Introduction

The common issue of anaemia in the older surgical population has a significant impact on postoperative morbidity and mortality. Anaemic patients frequently proceed to surgery without considered assessment and management of this risk factor for adverse outcome. The current mainstay of management for anaemia in the older surgical patient, allogenic blood transfusion, can contribute to negative outcomes and is increasingly avoided where possible. Physicians are often asked to advise on optimizing anaemic patients preoperatively. The advice provided varies widely between physicians and anaesthetists or surgeons managing the same patient group. All those involved in preoperative optimization and postoperative management of older surgical patients should ensure that a considered and consistent approach to anaemia is part of routine management.

To date, there is a lack of a narrative synthesis review comprehensively drawing on literature from both elective and emergency surgical populations. This review aims to provide the clinician with a summary of the causes, implications and potential treatments for the management of anaemia in the older surgical population. A literature search was conducted in PubMed using search terms 'preoperative anaemia', 'postoperative anaemia' and 'surgery' combined with 'blood transfusion', 'intravenous iron' and 'erythropoietin'.

Definition and prevalence of anaemia

Anaemia is defined by the World Health Organization (WHO) as a haemoglobin (Hb) level of <13 g/dL in men and <12 g/dL in women.[1] The prevalence of anaemia increases with age but varies with subpopulation.[2] While < 10% of community dwelling over-65-year-olds are anaemic,[3] the older frailer nursing home population has a prevalence of anaemia of 48%.[4,5] Estimates of the prevalence of anaemia in the surgical population vary widely from 5% to 75%.[6–8] This variation is due to different definitions, types of surgical procedure, presence of malignancy, and emergency or elective presentation. Within octogenarians undergoing elective cardiac surgery, 40.4% of men were anaemic at presentation for surgery.[9] A similar prevalence (46%) was observed in emergency surgical patients with hip fracture.[10]

Aetiology of anaemia in older surgical patients

The causes of anaemia in older surgical patients are varied and relate to physiological ageing, the effect of co-morbidities and the surgical procedure itself.

Anaemia and ageing

Ageing is associated with dysregulation of proinflammatory cytokines, which negatively influence haemopoesis either through the inhibition of erythropoietin production or impaired erythropoietin receptor function.[11]

Anaemia secondary to iron or nutritional deficiency

Anaemia related to iron deficiency is common.[11,12] NHANES III data suggest that 35% of anaemia in over-65-year-olds in the United States is caused by deficiencies in iron, folate and vitamin B12.[13] In the developed world, iron deficiency anaemia is most commonly related to gastrointestinal blood loss from ulceration or malignancy.[13,14] Vitamin B12 and folate deficiency result from inadequate intake or reduced absorption.[15,16]

Anaemia of chronic disease

The older population commonly display multimorbidity, so it is unsurprising that they frequently develop the 'anaemia of chronic disease or chronic inflammation'. The pathophysiology of this condition is multifactorial and likely mediated by proinflammatory cytokines (interleukin-1 [IL-1], IL-6, tumour necrosis factor-α [TNF-α]).[11,17] These cytokines influence the secretion and action of erythropoietin, median red blood cell survival, progenitor apoptosis and iron processing.[11,18,19]

Haemoglobin and renal function progressively decline with advancing age.[11] Chronic kidney disease is an important cause of anaemia in the elderly[20] and primarily occurs primarily due to a decline in erythropoietin. As the glomerular filtration rate decreases, the prevalence of anaemia increases.[20] There is also emerging evidence describing the influence of cytokines in anaemia related to chronic kidney disease.[20]

Unexplained anaemia

Epidemiological work has shown that unexplained anaemia accounts for about one-third of anaemia in older people.[11–13,21–23] In confirmation of this epidemiological finding, a study using bone marrow analysis in an older anaemic population also found a lack of apparent cause for anaemia in a similar proportion of patients.[21]

Postoperative anaemia

Postoperative anaemia has multiple causes. It can result from pre-existing preoperative anaemia or occur secondary to traumatic or operative blood loss often worsened by haemodilution. Inflammatory cytokine release (IL-1, interferon-γ, TNF-α) after surgery can cause reduced gastrointestinal iron uptake, iron sequestration in macrophages, decreased erythroid response to erythropoietin and diminished erythropoietin production.[18,24,25] This results in less available iron for erythropoesis despite normal iron stores in the bone marrow macrophages.[25,26] All these factors can exacerbate postoperative anaemia.

Implications of anaemia on the older surgical patient

Within the older surgical population, anaemia has been shown to increase mortality, postoperative complication rates, length of hospital stay and worsen functional outcomes.[27–30]

Mortality

Preoperative anaemia (defined either by preoperative haemoglobin or haematocrit) is

independently associated with an increased 30- and 90-day mortality after various types of non-emergency non-cardiac surgery.[31–35] Using preoperative haematocrit from the NSQUIP database and based on clinical reasoning and existing literature,[8] anaemia was categorized as severe (21–25%), moderate (26–29%), mild (30–37%) or not anaemic (≥38%).[33] The adverse composite outcome of myocardial infarction, stroke, progressive renal insufficiency or death within 30 days of operation was more likely to occur in those with severe (odds ratio [OR] 1.83; 95% confidence interval [CI] 1.05–3.19), moderate (OR 2.19; 95% CI 1.63–2.94) and mild anaemia (OR 1.49; 95% CI 1.20–1.86) when compared to non-anaemic patients.[33] Unsurprisingly, this increased mortality was more significant in those with pre-existing cardiovascular disease.[31] Furthermore, this finding of increased mortality persisted even after patients with severe anaemia (Hb < 9.5 g/dL) and patients who received red cell transfusions were excluded from the analysis.[32]

Postoperative complications

Anaemia has a negative impact on medical postoperative outcomes, functional status and quality of life (QOL) in both elective and emergency surgical populations. Within elective cardiac and non-cardiac surgical populations preoperative anaemia is associated with increased risk of perioperative cardiac events, infective complications, respiratory failure, and renal and central nervous system adverse outcomes.[30,31,35] Furthermore, and particularly relevant to older surgical patients, a postoperative haematocrit of <30% in patients aged over 50 undergoing major elective non-cardiac surgery is an independent predictor of postoperative delirium.[36] This is important as delirium itself carries a risk of increased mortality, morbidity, longer length of hospital stay and higher chance of institutionalization.[37–39] In elective patients undergoing joint replacement, the effects of anaemia on QOL are mixed. Initial studies suggested that perioperative anaemia adversely affected QOL,[40–42] but this finding was not confirmed by two larger and more recent studies which showed no association between postoperative haemoglobin and QOL.[43,44]

In emergency patients following hip fracture, anaemia on admission confers a negative impact on postoperative functional recovery, length of hospital stay and readmission rate.[10,45,46] In the first three days following hip fracture surgery, a significant linear association is shown between higher haemoglobin level and improved functional status[29] (measured using the validated cumulated ambulation score[47]). Within this study, anaemia was an independent risk factor for inability to walk on the third postoperative day.[29]

While not universally observed,[48] the majority of the evidence suggests an association between preoperative anaemia and adverse postoperative outcome. This raises the question of whether treatment of the condition may contribute to poor outcome.

Red cell transfusion

Preoperative anaemia, postoperative anaemia and red cell transfusion are closely linked, so accurately identifying the independent effects of each issue can be problematic. Preoperative anaemia in surgical patients increases the chance of requiring allogenic red cell transfusion[49–52] which is itself associated with adverse effects.[49,52,53] Furthermore, red cell transfusion occurs more commonly in unwell patients, who are more likely to develop complications and die.[54,55]

Our understanding of red blood cell storage effects and the immunomodulatory effects of allogenic transfusion is improving. This has led to the exploration of the risk–benefit ratio of transfusion.[56,57] The results from observational studies are mixed. Studies from the adult intensive care, trauma and surgical populations assert that red cell transfusion is associated with increased morbidity and mortality and recommend conservative transfusion triggers.[58,59]

In contrast, two large retrospective studies report that while transfusion is associated with increased mortality if the preoperative haematocrit is between 30% and 35.9% with less than 500 mL blood loss, conversely in patients with over 500 mL blood loss or a preoperative haematocrit of less than 24%, transfusion may actually reduce mortality risk.[60] More recently, the same group concluded that, at an institutional level, hospitals with higher transfusion rates for significant perioperative blood loss (more than 500 mL) report reduced 30-day mortality rates.[61]

To address this controversy, three recent randomized controlled trials (RCT) have examined the impact of restrictive *versus* liberal transfusion strategies in patients undergoing cardiac[62] and hip fracture surgery.[63,64] Restrictive transfusion triggers are defined as haemoglobin of 8 g/dL or

haematocrit of ≥24% and liberal transfusion triggers as haemoglobin of 10 g/dL or haematocrit of ≥30%. These studies reported no difference in mortality between the restrictive and liberal groups suggesting that arbitrarily maintaining a higher haemoglobin level may not be beneficial.

In terms of morbidity, blood transfusion has been associated with increased rates of postoperative infection in both emergency hip fracture patients[65] and a mixed cohort of emergency and elective patients undergoing non-cardiac surgery.[66] Following hip fracture surgery, no difference was seen in functional status at 60-day follow-up (defined as inability to walk unaided across a room) in patients transfused using either the restrictive or liberal trigger.[63]

This may seem counter to the clinical experience of numerous physicians involved in the rehabilitation of older postoperative patients who often report the benefits of transfusion in enabling rehabilitation. Nevertheless, while results are mixed, given these data our usage of allogenic blood transfusion should be cautious instead focusing efforts on transfusion sparing approaches to managing anaemia in the older surgical patient.

Elective *versus* emergency surgery

A recent meta-analysis included randomized studies in both elective and emergency orthopaedic surgery to assess the impact of iron administration on morbidity and mortality. This analysis acknowledged concerns regarding randomization, concealed allocation, blinding, acceptable levels of compliance and use of intention to treat analysis. The paper concluded that while administration of iron conclusively raised haemoglobin level in comparison with placebo, overall there was no significant difference observed in postoperative morbidity, mortality, rate of volume of allogenic blood transfusion or length of hospital stay.[67] Treatment durations in the trials ranged from one to six weeks with follow-up periods lasting from 21 days to one year.

Elective surgery

Elective surgery offers the potential for preoperative optimization of haemoglobin levels before undergoing surgery. Treatment options include iron (orally or intravenously), vitamin supplementation, erythropoiesis stimulating therapy and autologous blood donation or cell salvage technology.

In elective orthopaedic patients, recommendations from an expert consensus panel (Network for Advancement of Transfusion Alternatives, NATA) suggest measuring haemoglobin at least 28 days prior to scheduled surgery to allow adequate corrective methods.[68] If anaemic (using WHO criteria), NATA suggest evaluation of iron status, renal function, and vitamin B12 and folate levels. Guidelines then advise gastroenterology or nephrology assessment, iron replacement therapy (oral or intravenous depending on intolerances and timeline before surgery) and vitamin B12 and folate replacement. When anaemia is related to chronic disease without other nutritional replacement possible, erythropoietic stimulating therapy is advised.[68] A small study of intra- and postoperative intravenous iron and erythropoietin administration in patients undergoing elective bilateral total knee replacement also showed favourable results on reducing postoperative transfusions in the six weeks following surgery.[69]

In elective colorectal[70] and gynaecological[71] surgical populations, contradictory results exist regarding the impact of intravenous iron in improving postoperative haemoglobin. The timing of iron administration in these studies differed (iron administered two weeks earlier in the hysterectomy study) which may account for the discrepancy in results with no benefit on postoperative haemoglobin seen in the colorectal group.

Furthermore, the use of oral iron after elective orthopaedic surgery appears to be ineffective at increasing postoperative haemoglobin without causing adverse side-effects.[72,73] This finding supports the assertion by NATA that assessment for anaemia should occur early in the preoperative pathway so that prompt treatment occurs.[68]

Other studies advocate the use of preoperative autologous blood donation with or without erythropoietin stimulating therapy in elective surgical groups. In general, autologous blood donation reduces rates of allogenic blood transfusion although the effects on other clinical outcomes have not been examined. This approach is labour intensive, expensive and inefficient, and is not routinely used within the UK.[51,74–80] Cell salvage is the process of collecting and then reinfusing blood shed from wound drainage peri- and postoperatively. Following initial safety concerns, more recent literature suggests that this may

represent a safe and cost-effective mechanism to reduce allogenic red cell transfusion.[81–83]

Emergency surgery

Most data on anaemia in emergency surgery comes from the hip fracture population. In contrast to elective surgery, these patients do not have a clear window for optimization particularly in light of current guidance advocating prompt surgical fixation of fractured neck of femur.[84]

While individual regimens for administration of intravenous iron and erythropoietin vary between studies, in general the initial dose of iron sucrose is administered preoperatively on the day of admission, with one or two subsequent doses given on consecutive postoperative days.

Two observational studies have prospectively examined the effect of intravenous iron in hip fracture patients. Both show a significantly lower rate of postoperative allogenic blood transfusion in the intervention groups.[85,86] Furthermore, one study showed a reduction in length of stay and 30-day mortality[85] and the other a reduction in postoperative infections in the intervention group.[86]

Two further observational studies prospectively examined the effect of combining intravenous iron with erythropoietin *versus* intravenous iron alone. Again there was a significant reduction in postoperative blood transfusion in the intervention groups.[26,87] The first, and smaller, of these studies also found a reduction in postoperative infections in the intervention arm,[26] yet this finding was not confirmed by a larger study which found no difference in postoperative cardiovascular complications, thromboembolic events, postoperative infections, length of stay, discharge destination or 30-day mortality between the two groups.[87]

In contrast to this observational work, a more recent RCT failed to show a difference in the primary outcome of postoperative transfusion in hip fracture patients given intravenous iron *versus* standard care (no intravenous iron). Although subgroup analysis suggested intervention in those with intracapsular fractures reduced postoperative transfusion rate, the small numbers mean that this finding warrants replication.[88] This discrepancy in the results between observational and randomized studies strengthens the case for definitive research.

More conclusively, the use of oral iron following hip fracture surgery appears ineffective.[72,89–91] A recent RCT assessing the effect of a six-week course of oral iron following hip fracture surgery concluded that there was no significant difference in length of hospital stay or one-year mortality rates between the iron and placebo groups.[92]

In summary, despite mixed results, the current evidence broadly supports the use of intravenous iron or intravenous iron and erythropoietin in reducing transfusion rates following hip fracture surgery. The acceptable safety profiles reported in these studies and the ability to administer iron or erythropoietin without delaying surgery suggests that such treatments should be employed clinically.

Patient blood management

Given the heterogeneity of approaches to improve haemoglobin levels and reduce use of red cell transfusion, coupled with the differing demands of elective and emergency surgical populations, the use of a set of guidelines or a standardized approach to management is appropriate. Patient blood management (PBM) is a programme or collection of approaches tailored to the individual patient aimed at minimizing the need for red cell transfusion and thus improving postoperative outcomes.[80,93–98] It centres on three 'pillars' (first, optimization of haemopoesis; second, minimizing blood loss and bleeding; and third, optimizing tolerance of anaemia) all of which have a preoperative, intraoperative and postoperative component. This approach is established in Australia and several centres in the USA but has been inconsistently adopted in Europe.[98] Recent work shows how this systematic approach to optimizing haemoglobin in surgical patients has been effectively and pragmatically implemented and appraised with improved 90-day postoperative outcomes within a UK centre.[99]

Conclusions

Proactively assessing and managing anaemia presents different challenges in the elective and emergency surgical groups. Despite these challenges, evidence is emerging for methods of 'transfusion sparing' intervention in order to optimize patients in the perioperative period. Given the current literature, we recommend employing patient blood management programmes incorporating the NATA guidelines when assessing patients prior to elective surgery and the use of intravenous iron possibly with

the addition of erythropoietin in the management of anaemic emergency surgical patients. Such interventions could be employed using guidance from the PBM approach. More research is required into the timing and methods of optimization in the anaemic surgical patient, particularly with respect to emergency surgery in order to provide definitive answers. A large RCT powered to robustly examine the effect of iron and erythropoietin on clinical outcomes after emergency surgery in anaemic subjects would help the formulation of a standardized approach to this common clinical scenario. Such work should weigh the benefit of optimizing anaemia against the need to expedite surgery within defined patient groups, in addition to evaluating cost-effectiveness.

Learning points

- Anaemia is common in the elderly surgical population.
- The commonest causes of anaemia in older people are iron deficiency anaemia and anaemia of chronic disease or inflammation. One-third of older anaemic patients have 'unexplained' anaemia.
- Anaemia is an independent risk factor for mortality, postoperative complication rates, length of hospital stay and poor functional outcomes in various elective and emergency surgical populations.
- Even 'mild' anaemia has a negative impact on mortality.
- Within the elective anaemic surgical population, prompt assessment for underlying cause, timely investigations and optimization using intravenous iron, nutritional supplementation, erythropoesis stimulating therapy and transfusion where necessary should be employed.
- Conservative or restrictive transfusion triggers are now recommended with evidence suggesting that such practice does not affect mortality or functional status postoperatively.
- Patient blood management programmes can be successfully implemented in the UK with benefits shown for surgical patients.
- Further work should evaluate the use and timing of iron and erythropoietin in large adequately powered RCTs on outcomes meaningful to older surgical patients.

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