Anaemia in hospital practice

This article describes the current problem of anaemia in hospital patients, functional iron deficiency and reviews the current roles of intravenous iron therapy. Attention to and correction of anaemia in the hospital patient may reduce the reliance for blood transfusion, with improvement in the patient's quality of life and outcomes.

Anaemia is common in hospital patients. Traditionally regarded as 'anaemia of chronic disease' as a consequence of concurrent illness or following surgery, current standard of care is blood transfusion. Alternatives for anaemia management are directed at correction of the underlying aetiology – vitamin B_{12}, folate or oral iron therapy. However, this approach will have little impact on the patient while he/she is in hospital and minimal effect on reducing the use of blood transfusion. Used initially in the management of renal anaemia intravenous iron can produce a rapid rise in haemoglobin. Although early products carried side effects, including risk of anaphylaxis, new preparations enable a total body iron replacement in a short period of time without the need for test doses or risk. The role for intravenous iron has expanded with recognition of functional iron deficiency in patients with heart failure, inflammatory bowel disease and patient undergoing surgery.

The problem of anaemia in hospital patients

The World Health Organization defines anaemia as insufficient red blood cell mass circulating in the blood. Anaemic thresholds are often quoted as the 5th percentile in a given studied population, <13 g/dl for men and <12 g/dl for women (Kraemer and Zimmerman, 2007). Anaemia is associated with impaired physical function, reduced quality of life, infection, patient morbidity and mortality (Spahn, 2010). Preoperative anaemia is common, affecting 30–60% of all patients undergoing major elective surgery (Shander et al, 2004). In the surgical setting anaemia compounds the stress of operation; anaemia is an independent risk factor for blood transfusion, inpatient complications, delayed hospital discharge and poorer recovery (Munoz et al, 2009).

Several authors have looked at the effect of anaemia on outcomes using the database from the American College of Surgeons National Surgical Quality Improvement Program. This program prospectively collects preoperative patient data, risk factors and laboratory results, also perioperative complications and 30-day postoperative outcomes for patients undergoing major surgery in more than 200 participating non-Veterans Affairs hospitals (www.acsnsqip.org). Wu et al (2007) looked at 310 311 veterans from 132 Veterans Affairs centres; they showed that anaemia (in predominantly elderly male patients) was associated with an increased risk of 30-day postoperative mortality and cardiac events in elective and emergency surgery.

In a smaller subgroup of 23 348 elective open and laparoscopic colectomies, Leichtle et al (2011) found that preoperative anaemia was associated with adverse composite outcome of myocardial infarction, stroke, renal insufficiency and 30-day mortality. In a detailed multivariate logistic regression analysis of 227 425 patients undergoing elective major non-cardiac surgery 69 229 patients had preoperative anaemia (Musallam et al, 2011). Preoperative anaemia was associated with a 35% increased risk for one major postoperative complication and 42% increased risk of death. This effect of preoperative anaemia was independent, adjusted for over 60 potential confounders and present for even mild anaemia.

Blood transfusion may be a poor treatment option

The current standard of care for anaemia in patients in hospital is blood transfusion (Gombotz et al, 2007). In 2008/9 1.86 million units of blood were transfused in the UK at a cost per unit of £130, an overall cost of provision to the NHS of £247.4 million. Audits repeatedly suggest an inflation of 256% in the cost of blood-related products in nearly 6 years (1995–2001), while the increase in blood donations is roughly 2% for the same period. The cost to the NHS from NHS Blood Transfusion is £130 for one unit of blood. However, the cumulative total NHS costs (e.g. nursing time, patient transport, treatment costs) are over £635 (Shander et al, 2010). In response to concerns over the impact of universal prion screening for blood products the NHS Blood Transfusion national commission has forecast an increase of £15–25/unit and nearly £41/unit in filtration charges from 2012 onwards (Bradburn, 2009).

Transfusion exerts immunological and immunosuppressive effects which include a decrease in T-cell production and natural killer cells and is associated with increased inflammatory response (Auerbach et al, 2008). The effect and outcomes from blood transfusion have been questioned. Glance et al (2011) found that intraoperative transfusion for severe anaemia (haemoglobin <10 g/dl) was associated with worse outcomes and mortality. Other small series in specific patient groups found similar results where blood transfusion was associated with increased postoperative sepsis and a worse patient

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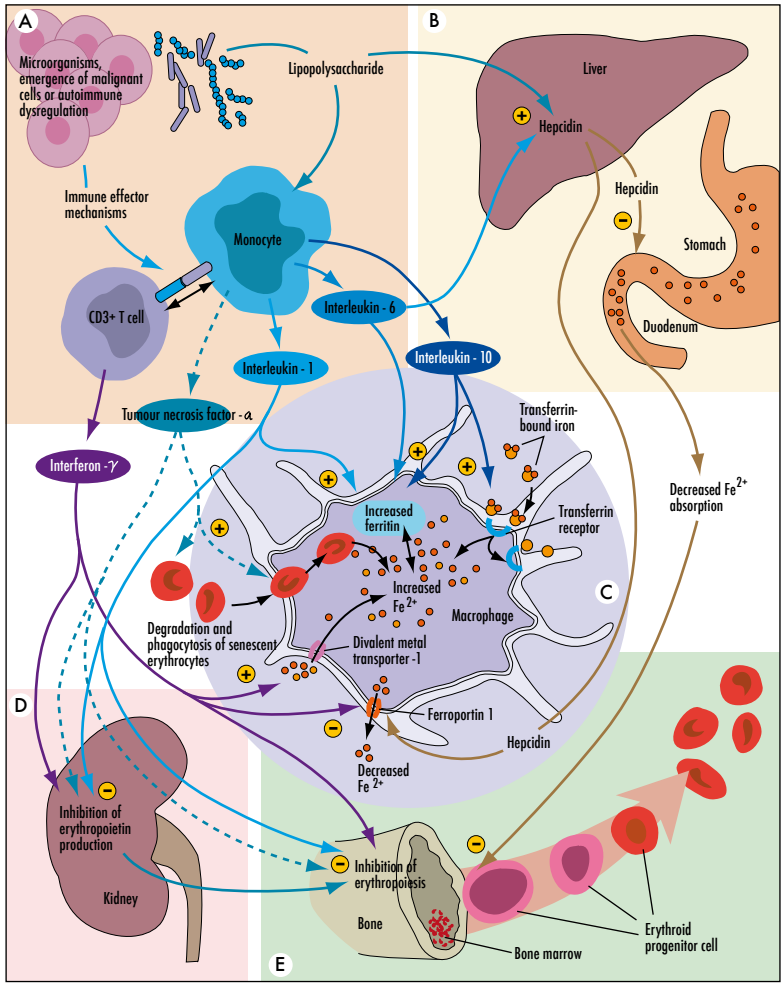
outcome (Dunne et al, 2002; Leichtle et al, 2011). In assessment of the National Surgical Quality Improvement Program database Bernard et al (2009) found that even one unit of blood increased risk of 30-day mortality, composite morbidity, pneumonia, and sepsis or shock. These data were validated in a further large analysis by Ferraris et al (2012) of just under one million patients; transfusion of a single unit of packed red blood cells increased the multivariate risk of mortality, wound problems, pulmonary complications, postoperative renal dysfunction, systemic sepsis, composite morbidity and postoperative length of stay compared with propensity-matched patients who did not receive intraoperative transfusion.

Figure 1. Pathophysiological mechanisms underlying anaemia of chronic disease. a. Invasion of microorganisms, the emergence of malignant cells or autoimmune dysregulation leads to activation of inflammatory pathways and cytokines release. b. Hepatic expression of the acute-phase protein hepcidin is activated, which inhibits duodenal absorption of iron. c. Ferrous iron (Fe2+) is taken up by macrophages. Transferrin receptor expression increases increasing transferrin bound iron into monocytes. In addition, activated macrophages phagocytose and degrade senescent erythrocytes. Expression of the macrophage iron transporter ferroportin 1 is downgraded, thus inhibiting iron export from macrophages and retention of iron. This leads to a decreased iron concentration in the circulation and thus to a limited availability of iron for erythroid cells. d. Production of erythropoietin in the kidney is inhibited. e. Differentiation and proliferation of erythroid progenitor cells is inhibited. In addition, the limited availability of iron and decreased biological activity of erythropoietin lead to inhibition of erythropoiesis and the development of anaemia. + = stimulation; – = inhibition. Adapted from Weiss and Goodnough (2005).



The longer term effect of blood transfusion has also been associated with an increased relative risk of cancer recurrence. A Cochrane review investigated the effects of allogenic blood transfusion and recurrence of colorectal cancer in 12 127 patients. This systematic review, last assessed as up to date in November 2010, concluded that there is indeed a moderate association between rates of allogenic blood transfusion and colorectal cancer recurrence, with an odds ratio of 1.42, and a statistically significant 95% confidence interval of 1.20–1.67. The conclusion was that allogenic blood transfusion should be restricted in its use in patients undergoing colorectal cancer resections with a curative intent (Amato and Pescatori, 2006).

The cause of anaemia in hospital patients

The cause of anaemia in this patient group is often multifactorial; caused by blood losses, nutritional deficiency (iron-deficiency anaemia), anaemia of chronic disease (cancer and/or inflammatory disease) or a combination of these aetiologies. Two main types of anaemia affect surgical patients, iron deficiency anaemia and anaemia of chronic disease; the latter is more common in chronically ill and hospitalized patients (Munoz et al, 2005). Anaemia of chronic disease can be difficult to diagnose, often being regarded as a diagnosis of exclusion. A key feature is a disruption of normal iron homeostasis initiated by a cytokine-mediated immune response, such as in chronic inflammatory disease, during infection or following surgery (*Figure 1*) (Nemeth et al, 2004; Weiss and Goodnough, 2005; Ganz and Nemeth, 2006).

Although anaemia is diagnosed by low haemoglobin blood indices including ferritin, mean corpuscular volume and mean corpuscular haemoglobin define the cause of anaemia. Iron deficiency anaemia is classically defined as microcytic hypochromic anaemia. However, in cases of chronic disease or inflammation ferritin may be elevated as part of the acute phase response. This has been recognized and definitions of absolute and functional iron deficiency proposed instead of iron deficiency anaemia or anaemia of chronic disease, others have suggested the term anaemia of inflammation (Nemeth and Ganz, 2009).

This problem of definitions was clarified in the FAIR–HF study of iron deficiency and heart failure; absolute iron deficiency was diagnosed when the serum ferritin level was less than 100 µg/litre and functional iron deficiency where ferritin was between 100 and 299 µg/litre and transferrin saturation was less than 20% (*Table 1*). In this group of patients mean C-reactive protein level was 7.46±5.34 mg/litre (Anker et al, 2009). There was no difference in response to intravenous iron therapy between

Table 1. Definitions of iron deficiency anaemia used in the FAIR–HF trial

Absolute iron deficiency	Depleted body iron stores
	Low serum ferritin (<100 ng/ml) or
	Transferrin saturation <20%
Functional iron deficiency	Inadequate iron supply to meet demand despite normal or abundant iron stores
	Normal or high ferritin levels
	Transferrin saturation <20%

From Anker et al (2009)

absolute and functional iron deficiency. Those treated with intravenous iron had a significant improvement in patient quality of life, disease status and 6-minute walk test compared to placebo.

Treating anaemia in hospital: why oral iron is not adequate

Oral iron is a common cheap and effective method to replenish total body iron stores in the elective setting. Oral iron is a treatment available in patients with iron deficiency anaemia. However, oral iron is poorly absorbed; several factors inhibit iron absorption (proton pump inhibitors, anti-inflammatory drugs, inflammation, and gastrointestinal disease including *Helicobacter pylori*. Further about half of patients have significant side effects of abdominal pain, constipation or heartburn. Compliance is also a great problem as only 20–40% of patients complete a full course of oral iron therapy.

Oral iron is absorbed in the duodenum at a rate of only 2–16 mg per day. A formula based on body weight and haemoglobin levels can be used to calculate the amount of iron needed to replenish iron stores – Ganzoni formula (*Figure 2*, *Table 2*) (Ganzoni, 1970). Ganzoni's calculations conclude that most patients will need between 1000 and 2000 mg of iron to replenish body reserves. Therefore oral iron can restore normal iron levels in 3–6 months – far too long in the surgical setting. Haemoglobin levels may in fact increase before the replenishment of iron stores, but the loss of an equivalent of one blood unit during surgery represents over 600 mg of iron stores and may compromise this lengthy treatment.

The main problem is that in surgical patients the underlying disease process and concomitant inflammatory response evoke mediators that reduce the intestinal absorption of iron. This occurs by both inhibition of erythroid colony growth and by suppression of endogenous erythropoetin production. These intestinal cytokines, associated with a high production of hepcidin, induce functional iron deficiency, which may incidentally find already depleted iron stores. Therefore, functional iron deficiency cannot be corrected by oral iron because intestinal iron absorption is decreased in the presence of normal iron stores (García Erce and Muñoz Gómez, 2005; Munoz et al, 2009).

Treating anaemia in hospital: why intravenous iron may work

Intravenous iron is the standard of care in patients with anaemia and renal failure. Its use has widened to routinely treat anaemia in patients with inflammatory bowel disease where oral iron is ineffective and the disease or inflammatory pathways block iron absorption from the gut (Evstatiev et al, 2011). Introduction of new intravenous iron preparations has enabled a single treatment to be given in a relatively short (15-minute) time without need for test dose, monitoring and reduced risk (*Table 3*). This ease of use has facilitated trials of intravenous iron to reduce blood transfusion in several areas of surgery. Data suggest intravenous iron may rapidly increase haemoglobin levels before operation and this may result in lower transfusion rates.

Figure 2. The Ganzoni formula used to calculate an individual's total iron deficit and consequently the dose of intravenous iron to be given. From Weiss and Goodnough (2005).

Iron dose (deficit) (mg) = body weight (kg)* x (150 - actual Hb) (g/litre) x 0.24† + 500 (mg)‡

* In patients with a body mass index >25 kg/m^2, a normalized weight (25 x height (m) x height (m)) will be used to calculate the iron deficit. † Factor 0.24 = 0.0034 (iron content Hb = 0.34%) × 0.07 (blood volume = 7% of body weight) × 1000 (conversion g to mg) ‡ Depot iron.

Table 2. Dose calculation for iron carboxymaltose

Haemoglobin	Body weight <70 kg	Body weight >70 kg
>10 g/dl	1000 mg	1500 mg
7–10 g/dl	1500 mg	2000 mg

From Evstatiev et al (2011)

Table 3. Current preparations of intravenous iron in the UK

Trade name	Generic name	Dose	Monitoring	Maximum dose	Infusion time
Cosmofer	Low molecular weight iron dextran	Ganzoni formula	Test dose	20 mg/kg	4–6 hours
Monofer	Iron isosorbide	Ganzoni formula	Yes	1000 mg per infusion	15–60 minutes
Venofer	Iron sucrose	200 mg	Yes	1000 mg per fortnight	2–5 minutes
Ferinject	Iron carboxymaltose	Haemoglobin/weight	No	1000 mg per week	15 minutes

In orthopaedics Theusinger et al (2007) used iron sucrose 900 mg intravenously over 10 days (4 weeks before surgery). The average haemoglobin increase was 1.0±0.6 g/dl (95% confidence interval= 0.2–2.2 g/dl), and the highest increase occurred 2 weeks after the start of iron therapy (P<0.0001). In 2004, Cuenca et al studied the effect of iron sucrose 200–300 mg in 55 patients 3 days before pertrochanteric hip fracture repair. End points of allogenic blood transfusion requirements and postoperative morbidity and mortality were compared with 102 controls. Iron sucrose reduced transfusion rates and also reduced postoperative infection, although there were no differences in 30-day mortality rate or length of stay. In a further study of 83 patients, intervention with a higher iron dose (3 x 200 mg/48 hours) combined with erythropoetin (40 000 IU) preoperatively showed a significant reduction in allogenic blood transfusion requirements (24% *vs* 271%; P<0.01) (Garcia-Erce et al, 2005). The Anaemia Working Group in España (Cuenca et al, 2006) published data on 129 patients undergoing total replacement of the knee who received iron sucrose (2 x 200 mg per 48 h, intravenous), with or without erythropoetin and a restrictive transfusion policy. This observational study suggested that this blood-saving protocol reduced allogenic blood transfusion rate and hastened the recovery from postoperative anaemia after total knee replacement.

In another observational study Bisbe et al (2005) assessed 27 patients scheduled for orthopaedic surgery. Of these patients, 20 cases received intravenous iron sucrose and erythropoetin and seven received iron alone. The results showed a haemoglobin increase of 1.7 g/dl in the group that received intravenous iron with little difference to those who also received erythropoetin. The authors concluded intravenous iron alone is useful for correcting preoperative anaemia and the use of erythropoetin should be restricted to cases in which correction of anaemia is refractory to the use of intravenous iron. Serrano-Trenas et al (2011) randomized 200 patients undergoing hip fracture surgery, of which one group (A= 100 patients) received standard treatment and another group (B= 100 patients) received intravenous iron sucrose (600 mg). Use of iron reduced transfusion requirements (41.3% in group A and 33.3% in group B). For patients affected with intracapsular fractures (45.7% required transfusion in group A, whereas 14.3% in group B; P<0.005).

Kim et al (2009) compared the efficacy of intravenous *vs* oral iron in the management of anaemia in patients with menorrhagia. Patients with severe anaemia (haemoglobin <9.0 g/dl) scheduled to undergo surgical treatment were randomized into two groups: the intervention group received iron sucrose three times a week, beginning 3 weeks before surgery, and the control group received oral iron (80 mg/day). The increase in haemoglobin was substantial in the intravenous iron compared to the oral group (3.0 *vs* 0.8 g/dl; P<0.0001). Ferritin levels were greater in the intravenous group (170.1 *vs* 4.1 µg/litre; P<0.0001) as well as the rate of patients achieving targeted haemoglobin levels (76.1% *vs* 11.5%; P<0.0001).

Diez-Lobo et al (2007) looked at iron deficiency before total abdominal hysterectomy. Intervention with iron sucrose (760±290 mg) resulted in an increase in preoperative haemoglobin (2.2±1.2 g/dl; P<0.0001), and lower transfusion rates (32% *vs* 0% respectively, P<0.001). In addition fewer women in the iron group were found to be anaemic 21 days postoperatively (23% *vs* 68%, P<0.01).

In general surgery, Munoz et al (2009) studied 84 anaemic patients scheduled for major elective surgery (30 colon cancer resections, 33 abdominal hysterectomies, and 21 lower limb arthroplasties). These patients received preoperative intravenous iron 3–5 weeks before surgery. Results concluded that the administration of intravenous iron (mean dose 440 mg) caused an increase in haemoglobin levels of 2.0 g/dl (P<0.001) and corrected anaemia in 68% of patients. No life-threatening adverse effects were seen.

There remains a need for a randomized controlled trial on the role of intravenous iron in surgery to prevent blood transfusion (Beris et al, 2008) and trials in surgery are pending with randomized controlled trials planned in cardiac, general and orthopaedic surgery.

Conclusions

Anaemia is a common problem in the hospital patient. Blood transfusion is an expensive and potentially harmful therapy. Identification of functional and absolute iron deficiency in the hospital patient facilitates directed therapy and intravenous iron may offer effective treatment. Further studies are pending in this area. **BJHM**

KEY POINTS

- Anaemia is a common problem in hospital patients.
- There is a need to recognize and define anaemia.
- Iron deficiency may be functional.
- Intravenous iron therapy may benefit hospital patients.

Conflict of interest: none.

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