Anaemia management in surgery – an experience with service evaluation and introducing guidelines for anaemia management.

Dr E Todman, Dr R Rao Baikady
The Royal Marsden NHS Foundation Trust, London, UK.

What is anaemia?

As defined by the World Health Organisation (WHO), anaemia is gender specific and the diagnosis occurs when the haemoglobin level is < 13g/dl in men and < 12g/dl in women. There are three different types of anaemia – macrocytic, normocytic and microcytic, each with differing causes. There is a high prevalence of anaemia in the perioperative period varying greatly from 20-70%[1,2].
The most common cause of anaemia is iron deficiency, either as an absolute iron deficiency (e.g. chronic blood loss) or a functional iron deficiency (e.g. chronic inflammatory states), with the other causes being less frequent. Therefore the focus in the pre-operative setting is on identifying and treating this cause of anaemia.

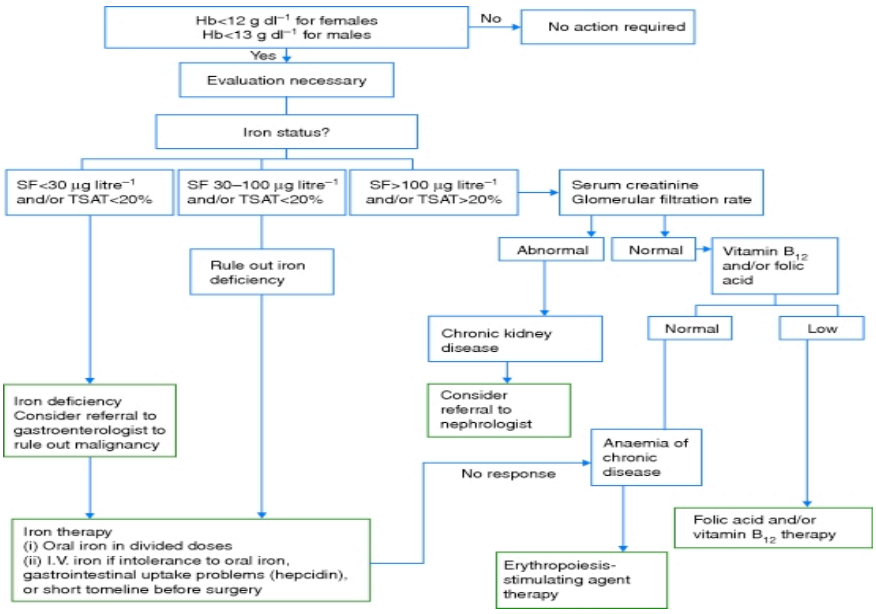
Types of anaemia in surgery

In the surgical population all types of anaemia may be encountered, which include, iron deficiency anaemia (IDA), anaemia of chronic disease (ACD), megaloblastic and pernicious anaemia as well as the red cell abnormalities such as sickle cell anaemia and thalassemia amongst others.
Within the pre operative surgical and anaesthesia setting some of these are treatable, including IDA and vitamin B12 and folate deficiencies and some need to be referred onto speciality teams e.g. haematology.
Iron deficiency anaemia is the commonest cause of anaemia worldwide, and therefore the commonest experienced within the pre-operative setting. It affects up to 5% of American women and 2% of American men[3].
The diagnosis of IDA depends on whether it is true iron deficiency or functional iron deficiency, however for the purposes of preoperative diagnosis a low Hb, a transferrin saturation (Tsat%) < 20% and a serum ferritin <30µg/l should be looked for.

Why treat anaemia?

Preoperative anaemia is one of the major predictors for perioperative allogenic blood transfusions in surgery with moderate to high blood loss[4]. There are also links between preoperative anaemia and increased morbidity and mortality of the surgical patient, as well as decreased quality of life within this population[2], this can lead to delayed recovery and increased hospital stay. The effects of pre-operative anaemia are compounded by intraoperative blood loss and possibly further aggravated by inflammation-induced inhibition of erythropoietin postoperatively. It is for these reasons that optimizing preoperative haemoglobin levels is included as part of the enhanced recovery surgical pathway[5].
There is also the importance of avoiding blood transfusions, in any patient, because of the general shortage of blood, not just in the UK but globally, but more significantly due to the early and late complications that are related to them. These include immunological, biochemical and infective complications, some of which can be severe and even life threatening.

The preoperative finding of anaemia and the further investigation must occur early enough to implement the appropriate management[6], to correct haemoglobin levels, before surgery proceeds. The following flowchart can be used for the assessment of reversible causes of anaemia in the pre-assessment setting, to ensure that this occurs.



Management of IDA in surgery - Oral vs IntraVenous (IV) iron.

Oral therapy for IDA is the first line choice for many patients, as it is significantly cheaper to intravenous options, and has a very good safety profile, but it will take several weeks (up to 12) to have an effective response and correct the iron deficiency.
Oral iron should be considered preoperatively for all major surgery if it is planned more than six weeks in advance. The recommended dose is Ferrous Sulphate 200mg three times a day for six to twelve weeks. Even post-operative oral iron can be considered for mild anaemia (Hb >10g/dl).
Unfortunately however it may be complicated by gastrointestinal side effects in up to 56% of patients, these include abdominal discomfort, nausea, vomiting, constipation and dark coloured stools[7], leading to poor compliance. Improved compliance with oral therapy has been sought by developing both enteric coated and delayed release forms of the drug. Unfortunately these have even less bioavailability than the original forms of the drug, with which 90% of the ingested iron is not absorbed[8].
Intravenous iron should be considered when there is a clinical need to correct anaemia and deliver iron quickly to the patient, such as in cancer surgery. It may also be appropriate for use in Jehovah's witness patients in the perioperative period and in those patients in whom oral therapy has been ineffective due to poor compliance or where daily iron loses from blood loss exceed the ability to replace iron stores. Intravenous therapy may also be required in ACD, where it appears to overcome the hepcidin induced block to absorption of iron from the gastrointestinal tract and the immobilization of stored iron[9]. It is worth noting however that there are some contraindications to intravenous iron therapy including:

1. Previous history of allergy to iron preparations or true iron allergy.
2. Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis)
3. Hypersensitivity to the active substance

4. History of symptomatic asthma, allergic eczema or other atopic allergy
5. Active infection (including sepsis, acute and chronic infection)
6. Decompensated liver disease (cirrhosis and hepatitis with abnormal liver function)
7. Rheumatoid arthritis with evidence of active inflammation

However iron infusions for IDA have been utilised in the peri-operative setting for a multitude of different surgical groups including gynaecological surgery, obstetrics, colo-rectal surgery, orthopaedic surgery, cardiac surgery and bariatric surgery. Muñoz et al demonstrated that a mean dose of 1000mg of preoperative intravenous iron in anaemic patients caused a significant increase in haemoglobin levels (2.0g/dl), with a standard deviation of 1.6g/dl and 58% of patients had resolution of their anaemia[1]. In addition Bisbe et al showed a higher final Hb and anaemia correction with more frequent attainment of iron replenishment in patients receiving ferric carboxymaltose compared with iron sucrose[6]. Hb increments were inversely proportional to baseline Hb levels as the endogenous erythropoietin response is greater at the lower Hb levels[5]. The results of the multicentre PREVENTT trial, to be undertaken soon will hopefully back up the findings of these studies.

Role of newer IV iron preparation

Historically intravenous iron therapy was associated with acute safety issues due to severe acute hypersensitivity reactions, resulting in a poor reputation for these products. This was related to the high molecular weight dextrans within the preparation. Newer intravenous preparations that are not bound to these dextrans have a much lower rate of adverse reactions. Three products have been developed recently which do not require a test dose, as required by older intravenous preparations. These products are Ferumoxytol, iron isomaltoside and ferric carboxymaltose. These can all be delivered rapidly providing high doses of iron replacement. All three have excellent safety profiles and can deliver total iron replacement (total dose infusion) in one infusion over 15-30minutes[10]. Iron isomaltoside is the newest of these agents and it enables a controlled slow release of iron and can be prescribed at 20mg/kg every 7 days if needed.
These total dose infusion products have been shown to achieve target Hb and ferritin levels more rapidly compared to either oral or regular small doses of intravenous iron[9]. They are also associated with statistically significant reductions in administered blood transfusions to patients who have received them[9].

Practical aspects of IDA management

Before treating iron deficiency anaemia the diagnosis needs to be made first. Iron deficiency causes morphological changes in red blood cells, which can be measured by red cell indices (part of the full blood count). Red blood cells become small (microcytic, MCV<76) and pale (hypochromic, MCH<27). Those patients with a combined iron deficiency anaemia and folate or Vitamin B12 deficiency may have a normal MCV.
Serum Ferritin which is a biochemistry blood test (red top sample), should be performed. A low serum ferritin (<100ug/L) is one of the sensitive laboratory test for iron deficiency but serum ferritin can be elevated by various types of chronic inflammation (including cancer) so a normal result does not exclude iron deficiency.

Transferrin saturation is another biochemistry blood test (green top sample) and the most specific test for diagnosing IDA. It is the ratio of serum iron and Total Iron Binding Capacity (TIBC). Normal values are 30 – 50 %. Transferrin saturation of <20% confirms iron deficiency.
Further tests that can be performed to confirm the diagnosis include serum iron that measures circulating iron levels bound to transferrin. Normal values are 9-30 µmol/L and Total Iron Binding Capacity (TIBC) nthat measures blood's capacity to bind iron with transferrin. Normal values are 35-81 µmol/L

Two differing forms of iron deficiency exist and these are:
True Iron Deficiency - Ferritin < 30 ug/L, Transferrin saturation < 20 %
Functional Iron Deficiency - Ferritin > 100 ug/L, Transferrin saturation < 20%

Once the diagnosis has been made of IDA then the choice of how to replace the iron needs to be made, this will be dependant on a couple of variables including:

1) Patient choice and the ability to deal with side effects
2) The speed of iron correction required i.e can surgery be delayed for non-cancer surgery
3) Are oral iron preparations likely to be ineffective as in anaemia of chronic disease and hepcidin up-regulation blocking iron uptake from the GI tract.

If intravenous iron infusion is considered appropriate then it can be administered in both the pre-operative setting or even in the post-operative setting. It is very simple to administer via a simple giving set over 15-60 minutes depending on which preparation is available, at a dose of up to 20mg/kg body weight, allowing for a total dose iron infusion (replaces all iron needed in the body in one hit)
Using the Ganzoni formula it is possible to calculate the iron deficit present and deduce the recommended intravenous iron dose:

Total iron needed = body weight x (Target Hb – Actual Hb) x 2.4 + 500
(mg) (kg) (g/dl) (mg)

This iron infusion can be administered in medical day units (MDU), clinical assessment units (CAU), all wards, theatres and theatre recovery areas where patients have intravenous access and monitoring is available.
Side effects to iron infusion are rare, with the commoner ones affecting between 1 in 100 to 1 in 1000 individuals and include:

1) Angioedema
2) Other allergic reactions including shortness of breath, flushing, body ache; especially chest and back ache and hypotension. Most of these reactions are self limiting.

Rarer reactions affecting 1 in 1000 to 1in 10000 individuals can include the following problems local reactions at the site of injection with redness, nausea, vomiting, cramps, chest pain, palpitations, blurred vision, hoarseness of voice, dizziness, temporary loss of consciousness, low blood pressure, sweating, head ache, body ache, altered mental state and seizure.

Most of these reactions are self-limiting and the treatment involves stopping the infusion. In a majority of cases the infusion can then be restarted 5 minutes after symptom resolution at a slower rate with no recurrence of the problem.
Other treatments that may be necessary in acute allergenic like reactions are oxygen, chlorphenamine and hydrocortisone

Cost effectiveness IV iron

Intravenous iron costs between £150-£200 per dose which is considerably more the oral iron tablets, which cost (INSERT NUMBER HERE). However this one dose will start to have an effect within 3-5 weeks of infusion and will continue to have an effect for up to 6 months. In comparison one unit of packed red cells which contains less iron costs between £140-180 pounds.
In addition to improving Hb levels and hence oxygen carrying capacity intavenous iron therapy may also improve muscle function (CHECK THIS OUT), lead to a better post operative recovery and by avoiding blood transfusion may lead to a shorter hospital stay[11].

Royal Marsden experience

The Royal Marsden hospital was keen to assess the benefits of intravenous iron infusion for IDA in their patients undergoing major oncological surgery. In this patient population IDA is very prevalent and delaying surgery to correct iron deficiency is very often not a clinical option.
A pilot study was therefore performed involving 33 patients with iron deficiency anaemia. Each patient was given 20mg/kg of iron isomaltoside either pre-operatively or in the immediate post operative period with very encouraging results. All bar one patient noticed an increase in Hb levels over time, with an average rises of 0.84g/dl at 2 weeks, 1.2g/dl at 3 weeks, 1.94g/dl at 4 weeks and 2.53g/dl at 8 weeks post infusion. One patient noted a transient body ache and the infusion was ceased. This data was presented at the Network for the Advancement of Transfusion Alternatives annual symposium in April 2013.
On the evidence of this pilot study drug approval was gained from the DTC at the hospital so that it is now part of the formulary.
After approval by the DTC, communication with various specialities was required to inform surgical teams, other anaesthetist and junior doctors of the availability of the treatment option.
The nursing staff at the hospital have been educated over a period of time in how to administer the intravenous iron, what monitoring is required and how to recognise and deal with any adverse reactions.
Finally local guidelines have been drawn up and implemented to assist members of medical staff to diagnose and manage IDA.

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