Management of Anaemia

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Haematology Consultant, GSTFT
POPS STUDY DAY
18TH March
Management of Anaemia

• Classification and causes of anaemia

• Iron deficiency anaemia

• Anaemia in surgical patients & management with POPS team.
# Normal Red Cell Indices

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td><strong>Haemoglobin g/dl</strong></td>
<td>13.5-17.5</td>
<td>11.5-15.5</td>
</tr>
<tr>
<td><strong>Haematocrit (PCV)%</strong></td>
<td>40-52</td>
<td>36-48</td>
</tr>
<tr>
<td><strong>Red cell count (x 10^{12}/l)</strong></td>
<td>4.5-6.5</td>
<td>3.9-5.6</td>
</tr>
<tr>
<td><strong>Mean cell Hb (pg)</strong></td>
<td>27-34</td>
<td></td>
</tr>
<tr>
<td><strong>Mean cell volume (fl)</strong></td>
<td>80-95</td>
<td></td>
</tr>
<tr>
<td><strong>Mean cell Hb concentration g/dl</strong></td>
<td>30-35</td>
<td></td>
</tr>
<tr>
<td><strong>Reticulocyte count (x 10^{9}/l)</strong></td>
<td>25-125</td>
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</table>
Red Cell Production

Bone Marrow

Red Blood Cells

Increase in Red Blood Cell Production

Increase in Response to Erythropoietin

Lack of Oxygen (Hypoxia)

Increase in Erythropoietin Production

Kidney

Erythropoietin

Pronormoblast

Basophilic Normoblast

Pryochromatic Normoblast

Orthochromatic Normoblast

Polychromatic Erythrocyte

Erythrocyte L
Anaemia

- Reduction in Haemoglobin concentration of the blood
  - Males adults: < 13.5g/dl
  - Females adults: < 11.5g/dl
  - 3 months-puberty: < 11.0g/dl
  - New born infants: < 15g/dl

- Clinical features depend upon
  - Speed of onset
  - Severity
  - Age
  - Hb dissociation curve
Anaemia – clinical features

- **Symptoms** – dyspnoea, SOBOE, weakness, lethargy, palpitations, headaches.
  - older patients – angina, cardiac failure, confusion.
  - visual disturbances – retinal haemorrhage

- **Signs** – general – pallor, mucous membranes (< 9g/dl)
  - hyperdynamic circulation, bounding pulse, cardiomegaly, systolic flow murmur.

- **Signs** – specific – particular types of anaemia – koilonychia with iron def. Anaemia, leg ulcers with sickle cell disease etc.
Causes of Anaemia

• Nutritional anaemia
  • Iron deficiency
  • Vitamin B₁₂ (pernicious anaemia)
  • Folate deficiency (megaloblastic anaemia)

• Anaemia due to reduced RBC production from bone marrow
  • Cancers such as leukaemia or secondaries
  • Bone marrow shut down - aplastic/drugs

• Haemolytic anaemia
  • Haemoglobinopathies
  • G-6 PD def/Hereditary spherocytosis
  • PNH

• Anaemia due to blood loss
  • Acute/chronic bleeding (GI bleeds, menorrhagia)
  • Auto-immunity
  • Infections/Fevers
  • Drugs

• OTHER
  • Anaemia of chronic disease - Renal disease
  • Pseudo-anaemia (pregnancy)
  • Anaemia of unknown cause.
# Classification of anaemia

<table>
<thead>
<tr>
<th>Microcytic Hypochromic</th>
<th>Normocytic normochromic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV &lt; 80fl</td>
<td>MCV 80-95fl</td>
<td>MCV &gt; 95fl</td>
</tr>
<tr>
<td>MCH &lt; 27pg</td>
<td>MCH &gt; 26pg</td>
<td></td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>haemolytic anaemias</td>
<td>Megaloblastic</td>
</tr>
<tr>
<td>Thalassaemia</td>
<td>chronic disease</td>
<td>B12, Folate def.</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Acute blood loss</td>
<td>Non megaloblastic</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td>Renal disease</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Sideroblastic anaemia</td>
<td>Mixed deficiencies</td>
<td>Myelodysplasia</td>
</tr>
<tr>
<td></td>
<td>Bone marrow failure</td>
<td>Aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td>Infiltration, chemo</td>
<td>Drugs</td>
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</tbody>
</table>
Investigation of Anaemia

- Clinical History - ? Underlying cause / disease
  Symptoms – time course
  Family history

- Examination – specific signs

- Laboratory Investigations – will depend on clinical picture
  FBC             Blood film – morphological changes
  Biochemistry
  Haematinics     Reticulocyte count
  Hb electrophoresis
  Special – Coombs test, haptoglobins, urinary haemosiderin
Investigative Pathways for Anaemia

- **Decreased MCV (Microcytic):**
  - Serum ferritin
    - Low → Hb electrophoresis
      - Iron deficiency
      - Thalassaemia minor
    - Normal
  - Haemolysis or blood loss

- **Normal MCV (Normocytic):**
  - Reticulocyte count
    - Increased
    - Haemolysis or blood loss
    - Marrow hypoplasia, leukaemia, infiltration
  - Not increased or abnormalities of other parameters

- **Increased MCV (Macrocytic):**
  - Serum folate
    - RBC folate
    - Vitamin B12 level
      - Folate deficiency
      - B12 deficiency
## Prevalence of IDA in England

*Health survey for England 2000*

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<thead>
<tr>
<th></th>
<th>Women 12g/dl</th>
<th>Men 13g/dl</th>
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<tbody>
<tr>
<td><strong>General pop</strong></td>
<td>10.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td><strong>Elderly (+75yrs)</strong></td>
<td>25%</td>
<td>18%</td>
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</tbody>
</table>
IDA causes

- Menstruation: 29%
- Aspirin/NSAID use: 8%
- Colonic carcinoma: 5%
- Gastric carcinoma: 8%
- Benign gastric ulceration: 5%
- Angiodysplasia: 13%
- Coeliac disease: 5%
- Blood donation: 5%
- Other: 5%
Iron Replacement
Iron Deficiency Anaemia

• Not a complete diagnosis in own right
• Iron indices – Low serum ferritin /iron / transferrin saturation.
• High TIBC (total iron binding capacity)
• ALWAYS need to identify underlying cause – Ca Colon – do not miss
• GI investigations anyone over 60 if no cause identified.
Iron Compartments

Iron-donating tissues and iron stores

- Macrophages 500 mg
- Hepatocytes 250 mg
- Gut
- Absorption \( \approx 1 \text{ mg/day} \)

Plasma (transferrin) 4 mg

- Ineffective erythropoiesis
- Loss \( \approx 1 \text{ mg/day} \)

Red cell haemoglobin 2500 mg

Bone marrow

Erythroblasts 150 mg

Tissues

- Iron-containing enzymes 150 mg
- Myoglobin 300 mg

Iron receptor tissues and functional iron compounds
Iron Absorption

Molecular pathways of iron absorption. The area enclosed in the dotted box refers to the uptake of iron from the plasma in the developing enterocyte in the intestinal crypt. Otherwise, the diagram refers to iron absorption by the villous epithelial cell. DMT1, divalent metal transporter 1; FPN, ferroportin; Hp, hephaestin; TF, transferrin; TFR, transferrin receptor.
Hepcidin Regulation

• Hepcidin, Hemojuvilin, Transferrin Receptor 2 and HFE produced in hepatocyte.

• ↑ plasma iron & inflammation stimulate Hepcidin synthesis.

• ↓ plasma iron, ↑ erythropoiesis & hypoxia inhibit hepcidin production.

• Hepcidin binds to ferroportin - ↑ destruction - ↓ iron absorption and release from macrophages and bone marrow.
Anaemia of Chronic Disease

Due to inflammatory cytokines affecting normal iron metabolism

- preventing ferroportin from releasing iron stores – liver produces increased hepcidin (IL6)
- Decreased ferroportin expression
- Blunted bone marrow response to Erythropoetin

ACD – associated with malignancies, inflammatory conditions – Rheumatois Arthritis/SLE/IBD/CRF

Treatment: Underlying disorder but may be combined deficiency so look for iron levels and treatment empirically may benefit anaemia.
Anaemia in Surgical Patients

  52% – Medical patients
  41% - Surgical patients
  8% - orthopaedic: THA, TKA and surgical hip
  7% - Obs & Gynae

- Anaemic patients
  ↑ ABT use
  ↑ Post –op infections
  ↓ physical functioning
  ↑ Length of hospital stay
  ↑ mortality

Spahn: Anaesthesiology 2010;113:482-95 2010
Anaemia in Surgical Patients

Epidemiology:
Elective TKA/THA – younger than Hip # pts
- 68.5 +/- 3.2 vs 79.1 +/- 1.8 yrs

Hb levels and definition of anaemia was variable – from < 13g/dl
- <10g/dl
-pre op 25% in elective THA/TKA & 50% Hip #
-post-op 51% THA/TKA & 87% Hip #

Weighted mean Hb levels ↓
-13.6 +/- 0.4 pre-op to 10.6 =/- 0.8g/dl post-op IN THA/TKA (3.0g)
12.5 +/- 0.2 pre-op to 8.2 +/- 2.1 g/dl post op in Hip# (4.3g)
Anaemia in Surgical Patients

Physical function

*Kehlet et al* Sig ↓ ability to mobilise within 3 days post op if Hb < 10g/dl

*Carson JL et al*: Observational study (5,793pt) – low post Hb independantly associated with shorter walking distance at time of discharge

Decline in instrumental activities of daily living at 3, 6, 9 and 12 months post op.

3 studies – No association.
Anaemia in Surgical Patients

**ABT**
Triggers vary
10-89% of patients
Units transfused – THA/TKA & Hip # - 2.3-2.6

**Infection**
*Dolan et al:2004, prospective study 225 pts THA*
Anaemia - ↑ post op UTI (28 vs 14% p=0.039)
Post –Op ABT rates 71% in anaemia vs 10.5% in non-anaemic patients -
Management of Anaemia in Surgical Patients

- 2 cohort studies

**Pre-op oral iron and iv iron** 4 weeks pre-op for Hip#

↓ need for ABT

↓ post op infection rate

↓ LOS

- 8 Studies - rHuEPO + oral or iv iron (+/- cell salvage/PAD)

↑ mean Hb 1.6g/dl

↓ ABT

↔ LOS & 30 day mortality outcomes

↑ improved QoL score.
EPO and Iv Iron in Surgical Patients

• rHuEPO regimes vary – single dose/multiple doses + iv iron
• Efficacy of combination in ↓ ABT & Safety of iv iron infusions demonstrated – Munoz et al 2010, Thomas et al 2009, Martinez et al 2005
• Issues
  Several preparations – dextrose and sucrose based compounds
  Clear patient pathway and protocols
  Education of health professionals
  Education of patients
Patient Listed for surgery (Orthopaedics)

*POPS Team

Waiting list

Pre-Assessment clinic

Haematology

- Clinical review for anaemia
- blood tests
- iron replacement
- additional test –GI if needed
- liaise with POPS team
"Good to have you with us, Farquhar. We could do with some fresh blood in this place."
The use of Erythropoietin (EPO) in adult patients prior to elective major orthopaedics surgery to reduce exposure to allogeneic blood transfusion: A pilot study.


Introduction

Allogeneic blood transfusion in the context of orthopaedic surgery is known to be associated with increased morbidity, mortality and prolonged hospital stay. Alternative peri-operative management strategies aiming to increment Haemoglobin (Hb) levels or conserve blood loss are now becoming important public health and clinical governance issues. The use of erythropoietin (EPO) has been reported to reduce blood transfusion requirements in major elective orthopaedic surgery. EPO has also been used for the treatment of anaemia associated with kidney disease or cancer treatment.

An audit carried out in 2006 at Guy’s and St Thomas’ NHS Foundation Trust showed that blood transfusion rates for major orthopaedic surgeries ranged from 19% - 65% for all hip or knee operations within a year period. Total Knee Replacements: 19% for primary & 37% for revision. Total Hip Replacements: 37% for primary & 65% for revision.

Therefore, it was agreed to fund this pilot trial of the use of EPO in selected patients prior to hip or knee surgery.

Methods

The objective of this pilot was to correct the Hb level of suitable candidates to above 13g/dl.

We aimed to recruit 30 consenting adults from the trust orthopaedics waiting list.

Erythropoietin (NeoRecormon®) was administered subcutaneously at weekly intervals on days 21, 14, 7 and 0 (surgery) to selected consenting patients.

40,000 units of Epo was prescribed for patients <90kg body weight) or 60,000 units in those >90kg.

Where indicated, intermittent intravenous iron (Venofer®) was administered to achieve a target ferritin > 100µg/l.

FBC, ferritin and blood pressure were recorded and monitored on each day of treatment.

Standard thromboprophylaxis was given as per trust guidelines.

Results

Data is presented on 23 recruits: 20 females and 3 males.

The median age of included patients was 74 years (range 39-90).

14 patients had total hip replacements
8 total knee replacement (3 primary; 5 revision)
1 acetabular cup replacement.

The number of EPO doses used per patient ranged from 2-4 (mean 3) depending on Hb at start of treatment and Hb response during the treatment. This study generated at least 2 additional visits to hospital per patient.

All patients received at least one dose of intravenous iron sucrose - Venofer® (median 2.0, range 1 – 3 doses).

Discussion

Overall the mean increment in haemoglobin was 1.8 g/dl (median 1.7; range 0.5 – 3.4). No adverse side events occurred from the administration of either EPO or intravenous iron in all treated patients.

- 21/23 patients underwent successful surgery
- 20 did not need allogeneic blood transfusion during or after their surgeries
- 1 patient received blood transfusion (4 units) during surgery due to severe haemorrhage. His Hb dropped from 13.1 to 7.1 g/dl.
- 2/23 patients treated but did not proceed to surgery.
- 1 patient was rescheduled by surgeon as she was a Jehovah Witness.
- 1 patient whose Hb incremented from 10.1 to 13.5 g/dl, felt dramatically better and she decided to cancel her operation.

Conclusions

From our preliminary results:

- We have demonstrated that the use of EPO & iv iron in adult patients prior to elective major orthopaedic surgery reduces the need for allogeneic blood transfusion.
- The treatment appears to be well tolerated.
- This requires a co-ordinated approach between the patients, orthopaedics/surgical, POPS and haematology teams for successful outcomes to be achieved

References

Ferric Carboxymaltose compared with Iron Dextran for the treatment of Iron Deficiency Anaemia
Richard Dillon, Ibrahim Momoh, Claire Harrison, Deepi Radia
from the Department of Haematology, Guys and St Thomas’ Hospitals NHS Trust, London UK

Background

Ferric carboxymaltose (FCM) (Ferinject®, Vifor Pharma) has recently become commercially available as a parenteral iron treatment. Advantages over existing preparations include no test dose and short infusion times (1g infusion: iron-dextran (ID), (CosmoFe®), Vitaline Pharma) 5h, iron-sucrose (Venofer®, Vifor Pharma) 8x2h, FCM 30min). Disadvantages include cost (basic NHS prices for 1g iron: iron-sucrose £70.80, ID £79.70, FCM £217.50). Little comparative clinical data is presently available. We present results from 82 patients treated with FCM and compare these with 44 patients historically treated with ID.

Methods

Patients were eligible for treatment in our unit if they had iron deficiency anaemia (IDA) and had been intolerant to or unresponsive to oral iron treatment or had imminent elective surgery. They were ineligible if they were aged <16 years or had renal failure (eGFR less than 30ml/min, in which case they were managed in a renal clinic). All patients were investigated as appropriate for the cause of iron deficiency. Treatment was delivered via a nurse-led service initiative. Haemoglobin (Hb) and serum ferritin were measured before and six weeks after treatment. Patients were treated with either FCM (500mg <60kg or 1g ≥60kg body weight) or ID (20mg/kg), depending upon which preparation was available in clinic at the time of treatment.

Results

Pre-treatment mean Hb was 9.0g/dL (95%CI 7.2-10.7) in the FCM group and 9.7 g/dL (8.3-10.9) in the ID group. Mean serum ferritin was 27mcg/l and mean cell volume (MCV) 76fl in the FCM group; mean ferritin was 23 mcg/l and MCV 79 in the ID group. One adverse event (hypotension) was noted with ID, and one (cutaneous eruption) with FCM.

At six weeks post treatment, mean Hb was 11.7g/dL in the FCM group and 11.1g/dL in the ID group (p=0.04). Mean ferritin was 221mcg/l and MCV 83fl after FCM; mean ferritin was 171mcg/l and MCV 85fl after ID, these differences were not statistically significant.

The mean increase in Haemoglobin from baseline was 2.7g/dL with FCM and 1.4g/dL with ID (p=6x10^-3). The mean increase in serum ferritin was 149mcg/l in both groups; the increase in MCV was 7fl with FCM and 6fl with ID, this difference was not statistically significant.

Conclusions

Ferric carboxymaltose appears safe and effective as a treatment for iron deficiency anaemia and resulted in a greater increase in haemoglobin at six weeks than iron dextran in this group of patients. The cost of FCM is higher although reduced infusion times may result in staff cost savings compared with existing preparations.
Don’t forget other Anaemias

Blood film
Macrocytes & hypersegmented Neutrophils – B12 & Folate Deficiency

Bone Marrow – megaloblastic anaemia

Jaundice

Spherocytes/NRBCs/Polychromasia

Intravascular Haemolysis - PNH
B12/Folate in Diet
Thank you.
Any Questions?