IV Iron: The Time is Now

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DISCLOSURE

Current Relevant Financial Relationship(s)
None
Iron Deficiency

• Common!
• Even without anemia detrimental
  – Fatigue
  – Restless legs
  – Alopecia
  – Pulmonary HTN
Functional Iron Deficiency

- Good iron stores but can’t deliver to red cells
- Diseases
  - Dialysis
  - EPO therapy
  - Heart failure
Oral Iron: The Good

• Cheap and easy!
• Effective
  – Once a day
  – With 500mg Vit C
  – With meat if feasible
  – No tea/coffee
Does Alternate-Day Dosing of Oral Iron Therapy Improve Iron Absorption?


**Daily Dosing 14 days**
- Fractional Absorption: 16%
- Total Absorption: 131 mg

**Alternate-Day Dosing 28 days**
- Fractional Absorption: 21%
- Total Absorption: 175 mg

**Comment:** Fractional absorption was better with alternate-day dosing, but total absorption would still have been better with daily dosing if that group had received 28 days of iron. Alternate-day dosing likely enhanced gastrointestinal tolerability.

But 28 days of daily iron = 262 mg absorbed
Oral Iron: The Bad

- GI Intolerance: 30-70%
  - Tolkien
    - Constipation: 12%
    - Diarrhea 8%
    - Nausea 11%

- Can lead to GI ulceration
  - GI blood loss increase 3.4x with pills
Oral Iron: The Bad

• Doesn’t work
  – Functional iron deficiency
  – Pace of blood loss > 10-20ml/day
  – Issues with GI track
Response to Oral Iron

- Best predictor of response is rise in hemoglobin by 1 g/dl in two weeks
Parental Iron Therapy

• When to use
  – Refractory to oral iron
  – Unable to take oral iron
  – Inflammatory bowel disease
  – Cannot keep up with blood loss
  – Severe anemia with quick response needed
Celiac Disease

- Common in whites

- Mechanism
  - Blood loss
  - Villous atrophy
  - Inflammation

- Even with gluten free diet may have persistent refractory iron deficiency
Inflammatory Bowel Disease

- Never give oral iron!
  - Worsens
    - Microbiome
    - Quality of life
    - Inflammation
Bariatric Surgery

- Bypass iron absorption
- Decrease iron intake
- Lack of stomach acid
- Obesity impairs iron absorption
Gesquiere et al, *Obesity Surgery* 2014;24:56-61
Functional Iron Deficiency

- Dialysis
  - IV iron: less need for EPO
- Heart failure
  - IV iron: less hospitalization, increase exercise ability
IV Iron in Dialysis


2141

PROACTIVE

Adults with ESKD
On hemodialysis ≤ 12 months
Ferritin < 400 µg/L TSAT < 30%
Receiving ESA

IRON SUCCROSE 400 mg
HELD IF ABOVE Monthly labs Ferritin 700 µg/L TSAT 40%

29,757 IU
Median monthly ESA dose
29%
Composite Primary Outcome: Death, MI, Stroke, Heart Failure
967 Total RCC units transfused

1093

REACTIVE

IRON SUCCROSE 0-400 mg TO MAINTAIN Monthly labs Ferritin 200 µg/L TSAT 20%

38,805 IU
Median monthly ESA dose
32%
Composite Primary Outcome: Death, MI, Stroke, Heart Failure
1122 Total RCC units transfused

What is IV Iron

- Free iron very toxic
- IV iron preparation “coated” with carbohydrate
- Uptaken by macrophages to increase iron stores
The diagram illustrates the history of intravenous iron (i.v. iron) use, showing the evolution of iron formulations from 1947 to 2000, with a focus on the risk assessment of each formulation:

1947: Fe-Saccharide
1954: Fe-Dextran (HMWD) - high risk
1991: Fe-Dextran (LMWD) - low risk
1999: Fe-Gluconate
2000: Fe-Sucrose

From 2009 onwards, new formulations have been introduced, including:

- >2009: Ferumoxytol
- “New” Fe-isomaltoside
- Fe-Carboymaltose

The diagram also depicts the structure of the iron formulations, with Fe\(^{3+}\) oxyhydroxide as the polynuclear core and a carbohydrate shell as the stabilizer. Each compound has a unique moiety that is highlighted in the diagram.
### Fe (III)-oxyhydroxide/oxide cores

#### Carbohydrate shell

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Carbohydrate shell</th>
</tr>
</thead>
<tbody>
<tr>
<td>InFeD</td>
<td>Low molecular weight dextran</td>
</tr>
<tr>
<td>Ferrlecit</td>
<td>Gluconate</td>
</tr>
<tr>
<td>Venofer</td>
<td>Sucrose</td>
</tr>
<tr>
<td>Ferinject</td>
<td>Carboxymaltose</td>
</tr>
<tr>
<td>FeraHeme</td>
<td>Polyglucose sorbitol carboxymethyl ether</td>
</tr>
<tr>
<td>Monofer</td>
<td>Isomalto-oligosaccharides</td>
</tr>
<tr>
<td>Maltofer</td>
<td>Polymaltose</td>
</tr>
</tbody>
</table>
Ferric carboxymaltose

α-amylase
Partial enzymatic degradation of the shell

Complete (enzymatic) degradation of the carbohydrate shell

Endolysosome

Steap3

DMT1

Labile iron pool

Hepcidin

FP

Hephaestin

Extracellular medium

Ceruloplasmin

Transferrin
IV Iron: Preparations

- Iron MW Iron Dextran: INFeD
- Iron Sucrose: Venofer
- Ferric Gluconate: Ferrlecit
- Ferumoxytol: FeraHeme
- Ferric Carboxymaltose: Injectafer
- Ferric Derisomaltose: Monoferric
Iron Salts

- Ferric Gluconate (Ferrlecit)
- Iron Sucrose (Venofer)
- Need multiple doses!
- Higher levels of labile iron
- Best for dialysis/EPO
Labile Iron Content in Parenteral Iron Products

Iron Dextran

• LMWID only form
  – HMWID too toxic
• Total dose replacement
• “One stop shopping”
  – One gram in one hour
• Cheapest iron
Ferric Carboxymaltose

- 750mg dose in US, 1gram in Europe
- Standard dose is 750mg x 2 one week appear
- Hypophosphatemia common
- Most expensive iron
Ferric Carboxymaltose

- High incidence hypophosphatemia
  - <2.0 mg/dl: 50 - 70%: <1.3 mg/dl, 10.0%
  - Osteomalacia reported
- Raises FGF-23 levels
- Can last 4-12 weeks
Ferumoxytol

• Also MRI contrast agent
  – Need to warn radiology for 3 months
• Early dosing 510mg over 17 seconds
  – High rate of reaction
• Current is 510mg over 15 minutes x 2
• Increasing experience with 1020mg
  – Insurance won’t pay! 😞
Ferric Derisomaltose

- FDA approved 5/2020
- Not widely available yet
- 1000mg over 20 minutes
- Cost: ???
Reactions

• Complement mediated pseudo-allergy
• Drug nonspecifically activates complement
  – Similar to rituximab etc.
• True anaphylaxis very rare
  – Negative tryptase > 300 reactions
Implication

• No value test dose
• Premedication often doesn’t help
• Diphenhydramine makes things worse
• Treat as infusion reaction not allergy
• Studies show risk same with all iron preparations
Safety

- Minor infusion reactions common (~1-2%) but true anaphylaxis very rare
- Death rates (per 100,000 Medicare)
  - INFeD 0.8 (0-1.9)
  - Ferrlecit 6.3 (1.3-1.4)
  - Venofer 6.6 (3.1-9)
  - FeraHeme 3.5 (0-7.8)
OHSU Data

• Iron dextran vs ferumoxytol
• N = 606
• Any reaction: 2.28% vs 2.78%
  – Stopped infusion: 0.7% vs 0.6%
Infections

- RCT show no long term infection risk with IV iron
- Unease giving in acute infection but no data
Intravenous iron dosing and infection risk in hemodialysis patients: a pre-specified secondary analysis of the PIVOTAL trial

**METHODS**

- Incident HD
- Ferritin <400 µg/L
- TSAT <30%
- IV iron sucrose
- N=2141

**RESULTS**

<table>
<thead>
<tr>
<th></th>
<th>Proactive high-dose</th>
<th>Reactive low-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any infection</strong></td>
<td>HR: 0.98, p=0.80</td>
<td>45.5%</td>
</tr>
<tr>
<td><strong>Hospitalization for infection</strong></td>
<td>HR: 0.99, p=0.92</td>
<td>29.3%</td>
</tr>
<tr>
<td><strong>Death from infection</strong></td>
<td>HR: 1.04, p=0.84</td>
<td>3.91%</td>
</tr>
</tbody>
</table>

- 400 mg/mo
- Only administered if:
  - Ferritin ≤400 mg/mo
  - TSAT ≥40%

**Median follow-up 2.1 years**

- 46.5%
- 29.6%
- 4.21%

- During infection (investigator judgment)

Risk of a first cardiovascular event was strongly associated with an infection-related event in the prior 30 days

**CONCLUSION** A proactive, higher dosing IV iron protocol did not affect infection incidence in a large HD population.

doi: 10.1681/ASN.2019090972
<table>
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<tr>
<th>Iron</th>
<th>Cost</th>
</tr>
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<tbody>
<tr>
<td>Ferric gluconate (Ferrlecit)</td>
<td>$600 (+2000)</td>
</tr>
<tr>
<td>Iron sucrose (Venofer)</td>
<td>$432 (+2000)</td>
</tr>
<tr>
<td>Ferumoxytol (FeraHeme)</td>
<td>$2571 (+500)</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Injectafer)</td>
<td>$2640 (+500)</td>
</tr>
<tr>
<td>Iron dextran (INFeD)</td>
<td>$350</td>
</tr>
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</table>
Our Approach

- 1000mg of LMWID over one hour
- Test ferritin in one month
- Goal > 50ng/dl (100ng/dl)
- Monitor every 3-4 months
## IV Iron Dosing

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Recommended Dose</th>
</tr>
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<tbody>
<tr>
<td>LMW Iron dextran</td>
<td>1000mg over 1 hr</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>510mg x 2 or 1020mg over 15 min</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>750mg x 2</td>
</tr>
<tr>
<td>Iron isomaltoside</td>
<td>1000 mg over 20 min</td>
</tr>
</tbody>
</table>

Dosing formula inaccurate and not cost-effective
Refractory Iron Deficiency

• Patient is “refractory” to IV iron
• No getting enough iron!
• Frequent ferritin checks infusions
• Goal iron > 100 ng/dl
Iron infusions

Feeling tired due to iron deficiency? Intravenous iron infusions are a safe and effective way to quickly restore your body's iron stores and get you back to feeling 100%. Available at Warrandyte Road Clinic.
Bottom Line

- IV iron is safe and effective for patients who need it