Intravenous (IV) iron

1. Clinical trials referenced for bioavailability and side effects

(Westad et al. 2008)

128 anemic women who had recently given birth were given either 200 mg iron sulphate daily or 600 mg iron sucrose intravenously followed by 200 mg iron sulphate daily from week 5. The trial lasted 12 weeks, and the usual tests were done at 4, 8 and 12 weeks.

results

![Mean Hb (g/L).](image1)

Figure 2. Hemoglobin levels by treatment group at inclusion and after 4, 8 and 12 weeks. Columns are mean values and bars are standard deviations. No statistically significant differences between groups. Group A is the intervention group (iron intravenously) and group B is the control group (peroral iron).

![Ferritin levels by treatment group.](image2)

Figure 3. Ferritin levels by treatment group at inclusion and after 4, 8 and 12 weeks. Columns are mean values and bars are standard deviations. Group A is the intervention group (iron intravenously) and group B is the control group (peroral iron).

"Conclusion. Women who received 600mg intravenous iron sucrose followed by standard oral iron after four weeks, replenished their iron stores more rapidly and had a more favorable development of the fatigue score indicating improved quality of life."

"Adverse reactions due to iron sucrose were few, transient and minor (phlebitis, pain at injection site). The vast majority were related to use of oral iron. A total of 16 patients withdrew from the study as a result of adverse reactions, eight in group A and eight in group B. All 16 were on oral iron sulphate treatment and withdrew due to adverse reaction related to oral iron. The single most common reason for withdrawal was gastrointestinal problems like constipation and abdominal pain."
My summary

IV sucrose was significantly more bioavailable than sulfate. It appears one 600mg dose of IV iron sucrose was more effective than 4 weeks of 200mg sulfate every day. Also considerably less side effects.

*(Singh, Fong, and Kuperan 1998)*

A study of 100 pregnant women with iron-deficiency anemia. They were given either iron fumarate 200 mg three times a day for the duration of the study, or else one dose of IV Iron polymaltose. The amount of IV iron was calculated depending on their weight and deficiency. The outcome of treatment was compared at 36 wk, at delivery and at 6 wk postpartum (after the birth).

Results

"Our study shows that intravenous iron treatment with Ferrum Hausmann (iron dextrin) resulted in a significantly better level of haemoglobin (p<0.001) and also other parameters of iron status at 36 wk gestation compared with oral treatment (Table 2). The haemoglobin level remained statistically higher (p=0.002) for the intravenous group at delivery compared with the oral group. Again, at 6 wk postpartum, the haemoglobin level was significantly higher (p=0.025). Serum ferritin level, which is the best indicator of iron stores, was significantly higher (p<0.001) in the intravenous group than the oral group at 36 wk, and at 6 wk postpartum. This reinforces the observation that parenteral iron is able to replenish iron stores more efficiently, completely and at a faster rate than oral iron therapy."

<table>
<thead>
<tr>
<th>Table 2: Evaluation of treatment effect on haemoglobin level and other iron indices at 36 wk gestation</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
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<tr>
<td>± SD</td>
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<tr>
<td>Iron (mmol/l) ± SD</td>
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<td>Ferritin (mg/l) ± SD</td>
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<tr>
<td>transferrin (mg/dl) ± SD</td>
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<td>Zinc protoporphyrin (mg/gHb) ± SD</td>
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* This refers to ratio of geometric means.

side effects

"All women in the intravenous group reported good tolerance in contrast to about half those on oral iron. No side effects, such as fever, flushing, headache, vomiting, myalgia or arthralgia, were reported for the intravenous group. Various side effects such as nausea, vomiting, constipation and diarrhea, were reported for the oral group."

my summary

Not sure about the exact doses given for the IV iron, but the fumarate doses were extremely high so it was surely less than that. Showed the IV treatment as significantly more effective and with less side effects.
(Cançado and Muñoz 2011)
"Treatment with IV iron is clearly superior to oral iron and presents several advantages such as faster and higher increase in Hb levels and replenishment of body iron stores."

(Nagaraju et al. 2013) & (Nissenson et al. 2003)
These two studies I’ve mentioned in the HIP section. They both show that IV iron sucrose was more effective than HIP in kidney disease patients.

(Lyseng-Williamson and Keating 2009)
A study looking at side effects of IV iron Ferric carboxymaltose vs sulfate.

2. General information
This isn’t a type of iron but a method of administration, where the iron solution is injected into a vein. There is also the possibility of intramuscular injections and also blood transfusions for iron, but these aren’t as common so just looking at the IV method.

There are different types of iron used, but in general it is a core of ferric iron that is bound inside a carbohydrate shell. (Cançado and Muñoz 2011)

Here is a brief outline of the main ones

**Iron dextran** (ID) - one of the earlier ones that comes in high and low molecular weight. Good for being able to give large doses (up to 1000 mg) but needs to be watched closely for anaphylaxis reactions and needs a test dose. Not that many AE’s though for both. Low molecular weight (LMW)-ID (INFeD®) a little safer than HMW-ID (Dexferrum®)

**Ferric gluconate** (FG) (Ferrlecit) - safer than dextran. The recommended dose of FG is 125 mg given as a bolus or short infusion.

**Iron sucrose** (IS) (Venofer) - Like FG its really safe and no test dose needed. 15-30 min infusion for doses of 200-300mg. Commonly given as 100–200 mg IV doses. Max weekly dose of 600mg.
Iron polymaltose (Ferrum H®, Ferrosig®)
As well as being an oral supplement, this one is also an IV iron. Also seems to be called iron dextrin just to be confusing. It has similar stability and structure to dextran, but doesn’t have the same risk of anaphylactic side effects. Like dextran it can do large doses - 1000 mg–2500 mg takes about 5 hours. Might only be available in austria and nz, at least for IV. This is the one that I had I think.

NEWER ONES:
The y all have better safety profiles and the advantage of larger doses over shorter times. Maybe not available every country.

Ferric carboxymaltose (FCM) (Injectafer, Ferinject®)
A new single-dose preparation. 1000 mg can be given over 15 minutes. Available in most countries but maybe not US.

Ferumoxytol (FeraHeme®)
One of the newest to enter the U.S. Don’t think it’s available in Europe or Aus. It can be administrated as a relatively large dose (max 510 mg) in a rapid (< 20 seconds) session without test dose requirement. Safety similar to LMW-ID, FG and IS. Had some reports of cardiac disorders so still being watched.

Iron isomaltoside 1000 (Monofer®)
It can be given as a rapid high dose infusion of up to 2000 mg without the need of a test dose. Available eu but not the US yet I think.

STILL IN DEVELOPMENT
Soluble ferric pyrophosphate delivered via hemodiasylate is a new iron formulation in phase III development.

(Auerbach and Ballard 2010)

3. General safety and side effects

(Newnham et al. 2006)
“An Australian audit of the in hospital safety and tolerability of iron polymaltose identified no cases of anaphylaxis or other cardiorespiratory compromise in 401 infusions, and noted infrequent minor side effects during infusion.”
(Chertow et al. 2006)
"The absolute rates of life-threatening ADEs were 0.6, 0.9, 3.3 and 11.3 per million for iron sucrose, sodium ferric gluconate complex, lower molecular weight iron dextran and higher molecular weight iron dextran, respectively."

(Lyseng-Williamson and Keating 2009)
“Other safety concerns with intravenous iron preparations include the risk of transient capillary leak syndrome, which may result in hypotension and other symptoms, and the promotion of infections, as serum iron is an essential nutrient for proliferating microorganisms. The clinical significance of the potential effects of iron on inflammation and active infection are controversial. Further data on the safety of ferric carboxymaltose are awaited with interest.”

(Cançado and Muñoz 2011)
Talks about the safety profiles of various IV iron formulas
"The incidence of serious life-threatening anaphylaxis with IS is 0.002% versus 0.6-2.3% and 0.04% with HMW-ID and FG,"

(Auerbach and Ballard 2010)
Talks about various studies looking at the increased risk of infection from iron
"The risk, if any, of IV iron causing infection and related morbidity and mortality is probably very small. Clinicians should weigh this information with the well-established benefits of effective iron management and anemia correction, including decreased morbidity and improved quality of life."

My summary of safety
With IV iron there is the risk of an allergic reaction - an adverse drug event (ADE). The threat of ADE’s has greatly decrease in the newer Iron treatments. For Iron Sucrose the threat of a serious life-threatening anaphylaxis is 0.002% (Cançado and Muñoz 2011) or 0.6 per million (Chertow et al. 2006)
Although accidental overdosing isn’t likely with IV iron, there still is the effects of the stress on the body of too much. This is the same as with oral supplements, but because of the bigger doses with IV it makes sense that it’s more of a concern.
Iron is an important nutrient for many bacteria and also seems to cause oxidative stress. There’s a lot of uncertainty as to what if any negative effects this oxidative stress causes. There seems to be more evidence showing an increase of infections related to iron treatments (from both oral and IV), however the risk seems small.
Not suitable during first trimester of pregnancy.

4. Cost
Depends a lot on country, health system, type of iron etc.

Administration costs
IV iron that need to be administered in a hospital over many hours is obviously high. Small dose GP injections also get expensive when multiple visits are needed. Newer ones that just need one injection from a GP naturally have a lower administration cost
Pg18 of this pdf put administration cost at a range of 20Euro - 320Euro

Formula cost
Hard to get the costs as they're not generally available for public purchase. A rough idea of the new formulas:
Ferinject – 250Euro /1000mg (2013 prices) this pdf
Injectafer - $62/750mg (GoodRx site)
Monofer – NHS Prices, not sure if this has any subsides.
2 ampoules of 10ml (1000mg iron) £339.00 = £170/1000mg
FeraHeme - NHS price for 1 x 17ml vial is £65 = 510 mg iron
In US$/1000mg = $82 - $300

5. References used in this section
<http://dx.doi.org/10.1182/asheducation-2010.1.338>

<http://dx.doi.org/10.5581/1516-8484.20110123>

<http://dx.doi.org/10.1111/j.1778-428X.2012.01178.x>


<http://dx.doi.org/10.1111/j.1445-5994.2006.01156.x>


Singh, K., Y. F. Fong, and P. Kuperan, ‘A Comparison between Intravenous Iron Polymaltose Complex (Ferrum Hausmann®) and Oral Ferrous Fumarate in the Treatment of Iron