IS IV IRON SUCROSE SIMILAR SAFE FOR MY PATIENTS?

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Seoul, Korea
Is IV Iron Sucrose Similar (ISS) Safe for My Patients?

Clinical and non-clinical data suggest reduced efficacy and/or safety concerns with various ISS’s

Conclusion

ISS may affect stability of the iron complex, which can lead to difference in safety and efficacy
Benefits of IV Iron
Compare to Oral Iron Iron

- First choice option for treatment
- May produce gastrointestinal disorders
- Limited by
  - poor absorption
  - low efficacy
  - poor compliance

- Rapidly deliver to the bone marrow
- Repletion of iron store is rapid
- High doses may be administered
- Frequency of adverse events is low

IV iron increased hemoglobin
more rapidly, effectively, and convenient
than oral iron
• Blood business

**OBSTETRICAL HEMORRHAGE: INTRODUCTION**
Obstetrics is "bloody business." Although medical advances have dramatically reduced maternal mortality, hemorrhage was a direct cause of more than 17 percent of 4200 Pregnancy Mortality Surveillance System of the Centers for Disease Control and Prevention United Kingdom reported in the Confidential Enquiry into Maternal and Child Health (2008) reported that 12 percent of maternal deaths were caused by obstetric hemorrhage for admission of pregnant women to intensive care units (Gilbert, 2003; Hazelgrove,

• Anemia

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menorrhagia</strong></td>
<td>65 (34.4%)</td>
</tr>
<tr>
<td>GI Bleed, Bleeding Ulcer or Gastric Erosion</td>
<td>27 (14.3%)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>24 (12.7%)</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>20 (10.6%)</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>20 (10.6%)</td>
</tr>
<tr>
<td>Gastric Bypass</td>
<td>14 (7.4%)</td>
</tr>
<tr>
<td>Crohn’s Disease or Ulcerative Colitis</td>
<td>13 (6.9%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>AV Malformation</td>
<td>6 (3.2%)</td>
</tr>
<tr>
<td><strong>Fibroids</strong></td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Multiple Surgeries</td>
<td>4 (2.1%)</td>
</tr>
</tbody>
</table>

Surgical Patients Number Registered in the Center for Bloodless Medicine & Surgery at SCH University Hospital, Seoul
## Development of Iron Sucrose in Korea

<table>
<thead>
<tr>
<th>Year</th>
<th>Component</th>
<th>Dose</th>
<th>Price</th>
<th>Brand Name</th>
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<tr>
<td>1999</td>
<td>Ferric hydroxide sucrose complex <strong>Original</strong></td>
<td>540 mg/mL <strong>5 mL/ampoule (100 mg/ampoule)</strong></td>
<td>₩11,053 (≈$10.05) ₩8,842 (≈$8.04)</td>
<td><strong>Venoferrum®</strong> (JW Pharma, Vifor Pharma Ltd.)</td>
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<td>2007</td>
<td>Ferric hydroxide sucrose complex <strong>Generic</strong></td>
<td>540 mg/mL <strong>5 mL/ampoule (100 mg/ampoule)</strong></td>
<td>₩7,516 (≈$6.83)</td>
<td><strong>Annerum®</strong> (BMI Korea)</td>
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<td>2007</td>
<td>Ferric hydroxide sucrose complex <strong>Generic</strong></td>
<td>540 mg/mL <strong>10 mL/ampoule (200 mg/ampoule)</strong></td>
<td>₩11,272 (≈$10.25)</td>
<td><strong>Ferex®</strong> (Samyang Genex Bio)</td>
</tr>
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<td><strong>Ferrowel®</strong> (Hanwha Pharma Co.Ltd.)</td>
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IV Iron Treatment in IDA Patients at SCH University Hospital

Adjustment of dilution and administration time (per manufacturer recommendation)
IV Iron Treatment in IDA Patients at SCH University Hospital

- April, 2000
  - Adjustment and administration time (manufacturer recommendation)
- 2008
  - Addition of 10ml iron sucrose similar
- 2008
  - Addition of 100ml 0.9% NS
- 2010
  - Addition of 100ml 0.9% NS
- Jan. 2011
  - Adjustment of dilution and administration time (per manufacturer recommendation)
  - Dec. 2011
Adverse Events

• Continued – seemingly increasing in frequency
Adverse Events

- Continued – seemingly increasing in frequency

ISS discontinued at our site

Retrospective analysis to examine the true number of adverse events
Intravenous Iron in the Treatment of Postoperative Anemia Following Obstetric and Gynecologic Surgery

Mi Kyoung Kang, M.D., Seong Yun Bang, M.D., Ji Young Kim, M.D., Eun Hee Park, M.D., Mi Kyung Kim, M.D., Ku Yeon Choi, M.D., Jeong Jae Lee, M.D., Im Soon Lee, M.D.

Department of Obstetrics and Gynecology, College of Medicine, Soonchunhyang University, Seoul, Korea
Iron Sucrose:

polynuclear iron(III)-hydroxide core complexed with sucrose in water

Non-Biological Complex Drug
Original article

Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynecologic operative patients

Abstract

Objective
Severe iron deficiency resulting in anemia is a common problem during pregnancy and in menstruating women. Several choices for IV iron replacement therapies exist and increased pressures on budgets may require cheaper "iron sucrose similar" (ISS) to be used. In our practice, an iron sucrose similar (Ferrox; ISSwR) was introduced to reduce costs in the treatment of pregnant women or those planned for surgery. Post several months of use we observed increased rates of adverse events from patients and hence performed this analysis to confirm these findings.
Study Design

• Determine the rate of adverse events with ISS
• **Retrospective analysis** of inpatients treated over a period of 4 years
• Patients with IDA
  – Post-pregnancy: natural birth or Cesarean sections
  – Post-Gy surgery: myomectomy, hysterectomy, cystectomy and adnexectomy
• Data collected for all treated patients in an anonymous manner with data points focusing on **adverse events during and after injection of IV iron**
• Events from patients charts and all data double checked
## Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>IS&lt;sub&gt;ORIG&lt;/sub&gt;</th>
<th>ISS&lt;sub&gt;FRX-100&lt;/sub&gt;</th>
<th>ISS&lt;sub&gt;FRX-200&lt;/sub&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>169</td>
<td>210</td>
<td>279</td>
<td>0.536</td>
</tr>
<tr>
<td>Age (years) (95% CI)</td>
<td>38.0 ± 9.7 (36.5–39.5)</td>
<td>38.5 ± 10.8 (37.0–39.9)</td>
<td>39.1 ± 10.6 (39.9–40.4)</td>
<td>0.536</td>
</tr>
<tr>
<td>Planned operation</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Obstetric surgery</td>
<td>78</td>
<td>94</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Uterine surgery</td>
<td>76</td>
<td>74</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>42</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Baseline Hb (g/dL) before iron injection (95% CI)</td>
<td>8.8 ± 1.3 (8.6–9.0)</td>
<td>9.9 ± 1.7 (9.7–10.1)</td>
<td>10.3 ± 1.5 (10.1–10.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total iron doses (mg) (95% CI)</td>
<td>416 ± 184 (388.0–444.1)</td>
<td>498 ± 159 (476.4–519.8)</td>
<td>490 ± 198 (467.0–513.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Significantly different from IS<sub>ORIG</sub> group.

IS<sub>ORIG</sub>: iron sucrose originator (Venoferum); ISS<sub>FRX</sub>: iron sucrose similar (Ferex).
Results

Increased in adverse events with use of an ISS

The events were acute
Results

- Most events were considered relatively mild with minimal
- However it caused increase patient stress and reluctance for repeat treatment
Comparison of Physicochemical Characteristics

Table 2. Physicochemical characteristics of the iron sucrose similar Ferex (ISSFRX) compared to the USP specifications for iron sucrose injection and the shelf-life specifications of iron sucrose originator (ISORIG) injection.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>USP*</th>
<th>ISORIG †</th>
<th>ISSFRX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
<td>–</td>
<td>–</td>
<td>FRX05-07003</td>
</tr>
<tr>
<td>Year of analysis</td>
<td>–</td>
<td>–</td>
<td>2008</td>
</tr>
<tr>
<td>Characteristics</td>
<td>–</td>
<td>Dark brown, opaque, aqueous solution</td>
<td>Dark brown, opaque, aqueous solution</td>
</tr>
<tr>
<td>pH</td>
<td>10.5–11.1</td>
<td>10.5–11.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Titratable alkalinity (ml)</td>
<td>0.5–0.8</td>
<td>0.5–0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Turbidity point</td>
<td>4.4–5.3</td>
<td>4.7–5.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Molecular weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mw (Da)</td>
<td>34,000–60,000</td>
<td>34,000–54,000</td>
<td>38,100</td>
</tr>
<tr>
<td>Mn (Da)</td>
<td>≥24,000</td>
<td>24,000–36,000</td>
<td>28,900</td>
</tr>
<tr>
<td>P</td>
<td>≤1.7</td>
<td>≤1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Reduction potential (mV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe(III)/Fe(II)</td>
<td>–700 to –800</td>
<td>–700 to –800</td>
<td>–630</td>
</tr>
<tr>
<td>Fe(II)/Fe(0)</td>
<td>–1350 to –1450</td>
<td>–1350 to –1450</td>
<td>–1410</td>
</tr>
</tbody>
</table>

†Shelf-life specification for ISORIG (iron sucrose injection).
Mw, weight average molecular weight; Mn, number average molecular weight; P, Mw/Mn ratio.
Limitation and Questions

• Clinical efficacy could not be evaluated
  – Many patients only had Hb measurements prior to ISS / Venoferrum® and next measurement after surgery or pregnancy
  – Differences in patient baseline population
  – Reduced efficacy in ISS group¹

• Unknown if additional toxicities as other assessments not conducted
  – Animal studies: impact to heart, liver or kidney²

2. Toblli JE et al. Inflamm Allergy Drug Targets 2012
## Clinical Data Demonstrate Differences between IS and ISS’s

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Key Results</th>
</tr>
</thead>
</table>
| **Alejandro Martin-Malo et al.**  
*Nephrol Dial Transplant*  
2012 | Assessed effects of both Venofer and ISS during the hemodialysis session in percentage of cells with ROS production, ICAM-1 and percentage apoptotic cells | Significant *increase of oxidative stress in HD patients treated with ISS*:  
- The percentage of cells with reactive oxygen species production, ICAM-1 expression and apoptosis was significantly increased with generic iron compounds at T2 and T3 in comparison to the original iron sucrose (Venofer®) |
| **Rottembourg J et al.**  
*Nephrol Dial Transplant*  
2011 | Retrospective evaluation to assess the impact of the switch from the originator IS (Venofer®) to the ISS (FerMylan®) on Hb levels and iron parameters in CKD patients undergoing hemodialysis | Switch to an ISS was associated with:  
- Significant reduction in Hb level  
- Reduced iron indices  
- Increased IV iron and ESA consumption  

Potential clinical implications of decrease in Hb level and shorter proportion of time spent within target Hb in population receiving an ISS. Both preparations showed a comparable safety profile |
| **Stein et al.**  
*CMRO*  
2012 | 3 case reports of IBD patients switched from iron sucrose (Venofer®) to an ISS | Patients experienced *hypovolaemic dysregulation, urticaria, headache, peripheral edema post treatment with ISS.*  
No adverse effects previously recorded with iron sucrose (Venofer®) administration |

ROS, reactive oxygen species; ICAM-1, inter-cellular adhesion molecule-1; HD, hemodialysis  
CKD, chronic kidney disease; ESA: erythropoiesis stimulating agent  
*CMRO*, Current Medical Research and Opinion; IBD, inflammatory bowel disease
Iron Sucrose
- Non-Biological Complex Drug -

Starting materials
[Iron sucrose (e.g. FeCl₃ or Fe₂(SO₄)₃); Base(e.g. NaOH, Na₂CO₃ or NH₃)]

Purification procedures

Synthetic procedures

Concentrations of the reagents

pH of the reaction mixture at different stages of the synthesis

Reaction temperature

Reaction time

Modified from Professor Jacques Rottembourg, Presented at Fresenius Nephro Summit Berlin, 31 March 2012
Iron Sucrose

not fully standardized manufacturing process:
subtle structural modifications

- Release iron too rapidly into circulation
  - Oxidative stress
  - Inflammation
  - Endothelial damage
  - Hemodynamic alteration

Safety
Efficacy
Conclusions

- **ISS had more adverse events** compared to originator iron sucrose (Venoferrum®)
- **Iron reduction potentials** of ISS didn’t comply with the pharmacopeial specifications and didn’t have standardized manufacturing process
- **Subtle structural modifications** may affect the stability of the iron complex, which can lead to difference in safety and efficacy
- **ISS, copy of non-biological complex drug, should undergo a centralized approval process**, supervised by EMA and FDA.
Original article
Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynecologic operative patients

Abstract
Objective
Severe iron deficiency resulting in anemia is a common problem during pregnancy and in menstruating women. Several choices for IV iron replacement therapies exist and increased pressures on budgets may require cheaper “iron sucrose similar” (ISS) to be used. In our practice, an iron sucrose similar (Ferex, ISS$_{59}$) was introduced to reduce costs in the treatment of pregnant women or those planned for surgery. Post several months of use we observed increased rates of adverse events from patients and hence performed this analysis to confirm these findings.