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Is Iron Sucrose (Venofer) a Safe Treatment for People with Chronic Kidney Disease?

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Is Iron Sucrose (Venofer) a safe treatment for people with Chronic Kidney Disease?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this study is to determine if Iron Sucrose (Venofer) is a safe treatment for people with Chronic Kidney Disease.

STUDY DESIGN: This paper looks at three randomize controlled trials from 2001, 2007 and 2008.

DATA SOURCES: Randomized controlled trials that compared Iron Sucrose to Iron Dextran and Iron Gluconate were found using OVID, Cochrane, Medline and Pubmed.

OUTCOME MEASURED: Adverse reactions that were analyzed based on serious and non-serious reactions to the iron preparations. Adverse reactions were also self reported or observed by the same person for a minimum of one hour following infusion of iron therapy. Examples of serious adverse reactions included anaphylaxis and death whereas non-serious adverse reactions were reactions such as GI upset and headaches.

CONCLUSIONS: After reviewing all three RCT, Iron Sucrose (Venofer) is a safe iron preparation for treating anemia associated with CKD.

KEY WORDS: CKD, Iron Sucrose, Venofer, parenteral iron, allergy, iron replacement, anemia
Introduction

The diagnosis of Chronic Kidney disease has nearly doubled over the last ten years. Due to the increase in end organ damage from high blood pressure and diabetes, to name a few, the number of people diagnosed with CKD will continue to rise over the years to come.

One of the major co morbidities that is strongly associated with CKD is anemia. There are many causes of the anemia associated with CKD; however some causes still remain unknown. A few of the major causes of anemia associated with CKD are as follows: a deficiency in EPO, frequent blood draws, GI hemorrhages, poor nutrition, coagulation of the dialyzer for those on dialysis, and anticoagulation leading to a lack of iron storage. However, the deficiency in erythropoietin of those with kidney disease remains the most significant cause of anemia in those with renal insufficiency. Besides the deficiency in EPO, patients can already have a deficiency in iron stores due to their low protein diet and a reduction in GI absorption due to uremia. Therefore, the replacement of primarily EPO without sufficient iron replacement therapy will not suffice in correcting the anemia in these patients.

Iron deficiency anemia is found in about 20-40% of patients on hemodialysis. The human body contains about 2-4 g of iron. In a patient with chronic kidney disease, about 1-1.5 grams of iron is lost during one year of dialysis. To correct this imbalance, it is necessary to use supplements of iron, other than those of the oral route due to the lack of efficacy.

CKD is of relevance to physician assistants because 26 million Americans are affected and millions of others are at an increased risk of developing renal insufficiency. Because obesity is on the rise in America, co morbidities of obesity including hypertension and diabetes are also on the rise putting more people at risk for developing CKD. CKD is associated with high rates of morbidity and mortality, placing the patient in need of a good health care system.
CKD can be associated with a major source to health care costs. It is estimated that 35 billion dollars is spent each year on patients with CKD. Many of the expenses related to CKD are associated with hospital stays, dialysis costs, multiple medications and the treatments of CKD co morbidities. In 2005, it was estimated that only 6.6 and 1.2% of Medicare patients were CKD and end stage renal failure patients, but used 19.4 and 8.2 % of all Medicare funds. The NHANES study showed that the number of physician visits greatly increased between early stages of CKD with 4-5 visits and late stages of CKD and ESRD with 6-7 visits per year. It was also estimated that patients with late stages of CKD had 2 hospitalizations per year with 14 visits to the hospital.

CKD is a slowly progressing condition which is characterized by a decrease in the function of the kidneys (decrease in the glomerular filtration rate) leading to volume overload, hypertension, organ damage and uremia. The most common causes of CKD are hypertension and uncontrolled diabetes. CKD is treated by a number of variables, all of which are important in combination with each other in preventing the progression or slowing the progression of the disease state. These methods include the use of ACE inhibitors for control of hypertension, but also as kidney protection, diuretics, diet restriction, glucose control, parenteral iron replacement, EPO, dialysis and transplant.

Parenteral iron replacement therapy is being recommended in the treatment of anemia associated with CKD because oral iron supplementation has not shown to be effective. There are a variety of parenteral iron replacements, some of which include Iron Sucrose and Iron Dextran.

Objective

The goal of this review is to determine if iron sucrose (Venofer) is a safe treatment for people with chronic kidney disease.
Methods

The studies chosen were all forms of randomized controlled trials. The first study was a head to head, open label prospective RTC. The second; a prospective open label study and the third a double blinded RTC. The inclusion criteria included people with CKD who were anemic as a result of CKD, some also on hemodialysis. The subjects studied had either overt iron deficiency anemia or were already being treated with a form of iron therapy to maintain Hgb levels and prevent iron deficiency anemia. Iron sucrose (Venofer) was the intervention studied in which its safety was compared to two alternative forms of parenteral iron which included Iron Dextran and Iron Gluconate. The outcomes measured were several adverse reactions, looking at the safety parameters of each type of iron therapy. Common adverse reactions measured included: hypotension, pruritis, nausea, vomiting, fever, headache and urticaria.

After using Cochrane Database, I searched OVID, Medline and Pub med to find qualified articles. Qualified articles were based on relativity to the topic chosen and were all patient oriented evidence that matters or POEMs. Each article used was in English and all data used was published between 2001 and 2008. In order to locate the RTC’s needed, key words searched were ‘CKD’, ‘iron sucrose’, ‘Venofer’, ‘parenteral iron’, ‘allergy’, ‘iron replacement’ and ‘anemia’. Each article contained slightly different inclusion and exclusion criteria. However, all subjects studied had CKD, some in different stages of kidney disease so that patients on hemodialysis were included. Subjects excluded were those that did not have an anemia due to iron deficiency, previous hypersensitivity to iron replacement therapy or some form of allergy such as atopic allergy, asthma or eczema. Patients using a form of therapy to prevent allergic reactions, such as anti-histamines, corticosteroids or immunosuppressive agents were also
excluded from the study. Statistics included were P-values, Confidence Intervals, NNT, RRR, and ARR.

Table 1. Demographics and Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># pt</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokgoz 2007</td>
<td>Randomized, double blinded, controlled</td>
<td>60</td>
<td>21-80</td>
<td>Patients with end stage renal failure</td>
<td>The Hgb levels had to be below 10g/dl, transferrin sat below 20%, and serum ferritin level below 100mcg/L</td>
<td>0</td>
<td>75 mg of iron sucrose or Iron Dextran, diluted in 100 ml saline administered over 30 minutes.</td>
</tr>
<tr>
<td>Bahner 2001</td>
<td>Prospective, open randomized controlled trial</td>
<td>59</td>
<td>44-74</td>
<td>Hemodialysis for 3 months, rHuEpo therapy for min 4 mo, hemoglobin btw 9 and 12, serum ferritin btw 100 and 600 mcg/L, normal serum B12 and folic acid conc.</td>
<td>No infection, malignancy or surgery; No chronic inflammatory disease and no blood transfusions in the last 3 months.</td>
<td>4</td>
<td>Iron sucrose was given to 27 pt (250 mg diluted in 100ml of NSS, infused over 60 minutes once a month). Iron Gluconate was given to 28 pt (62.5 mg over 5 min 1X/week at dialysis)</td>
</tr>
<tr>
<td>Anirban 2008</td>
<td>Head to Head, open label, prospective randomized control trial</td>
<td>370</td>
<td>27-57</td>
<td>Adult CKD patients who were on conservative management or on renal replacement therapy</td>
<td>Iron overload, hypersensitive to iron preparations, NON- iron deficiency anemia, atopic allergy, eczema or asthma, liver problems, infections, inflammatory joint disease, steroids, a goal of &gt;1L/h volume removal</td>
<td>31</td>
<td>Iron dextran-100mg in 100ml NSS over 30min, Iron Gluconate-125mg diluted in 100ml NSS over 60. Iron sucrose-100mg diluted in 100ml of NSS over 15 min.</td>
</tr>
</tbody>
</table>

Outcomes Measured
The outcomes of each study were the occurrences of adverse drug reactions. The adverse drug reactions measured had slightly different ways of being monitored. *Bahner et al* measured adverse reactions based on observation of the patients during the trial period and then self reported adverse reactions by the patient. Patients also had the opportunity to fill out questionnaires about the adverse reactions they were having. *Anirban et al* measured outcomes based on timing of drug administration such as adverse reactions at time of test dose, time of infusion and within the minutes after infusion and then again at 48 hours after. *Sav et al* measured outcomes by having each subject observed by the same person for an hour after infusion of iron therapy.

**Results**

In the study completed by *Anirban et al*, the efficacy of parenteral iron replacement is not quantified. However, *Anirban et al* states that the efficacy of all offered iron therapies are equivocal in nature, but the adverse event profile of each iron therapy is of concern. *Sav et al* also refrains from discussing efficacy of iron replacement. In comparison, *Kosch et al* discusses efficacy of two iron supplements, Iron Dextran and iron sucrose. The study concludes that from baseline to 6 months of time, the efficacy of both parenteral supplements is equivocal and that there is no statistically significant difference in the hemoglobin level, transferrin saturation and ferritin levels. While there is not a significant difference in comparison between the two forms of iron replacement, both iron sucrose and Iron Dextran had an increase in ferritin and transferrin that was statistically significant with a p value of less than 0.05. This was proven based on comparison of baseline values and values after treatment at the 6 month mark. Moreover, it appears that the decrease in hypochromic RBC is greater with the Iron Gluconate therapy,
however, this is not the case due to the factor that the baseline for the hypochromic RBC group’s baseline was much higher.

Table 2. Percent Mean Change comparing Iron Sucrose to Iron Gluconate

<table>
<thead>
<tr>
<th></th>
<th>Iron Sucrose (Baseline)</th>
<th>Iron Sucrose (After tx)</th>
<th>% mean change</th>
<th>Iron Gluconate (Baseline)</th>
<th>Iron Gluconate (After tx)</th>
<th>% mean change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.34</td>
<td>11.43</td>
<td>0.8%</td>
<td>11.33</td>
<td>11.42</td>
<td>0.8%</td>
</tr>
<tr>
<td>Ferritin</td>
<td>412</td>
<td>650*</td>
<td>58%</td>
<td>369</td>
<td>650*</td>
<td>76%</td>
</tr>
<tr>
<td>Hypochromic RBC</td>
<td>6.3</td>
<td>4.6</td>
<td>27%</td>
<td>10.8</td>
<td>5.2</td>
<td>52%</td>
</tr>
<tr>
<td>Transferrin Sat</td>
<td>21.9</td>
<td>33.3*</td>
<td>52%</td>
<td>25.7</td>
<td>34.4*</td>
<td>34%</td>
</tr>
<tr>
<td>White Cell Count</td>
<td>7.3</td>
<td>7.7</td>
<td>5%</td>
<td>7.3</td>
<td>7.2</td>
<td>Decrease 1%</td>
</tr>
<tr>
<td>Platelets</td>
<td>223.8</td>
<td>250.5</td>
<td>12%</td>
<td>227.6</td>
<td>230.3</td>
<td>1%</td>
</tr>
</tbody>
</table>

*= p value < 0.05

Sav et al compared the safety of Iron Sucrose and Iron Dextran. The adverse reactions anticipated were: hypo or hypertension, chest pain, skin reactions, nausea, vomiting, flushing, myalgia, syncope, headache, fever, bronchospasm, paresthesias and dyspnea. These were considered early reactions. Late adverse reactions examined were considered as adverse reactions occurring within 48 hours of administration of the iron therapy. The p value was greater than 0.05 meaning that there was no significant difference in the safety of either Iron Sucrose or Iron Dextran. While no serious reactions occurred, the patients who were using Iron Sucrose reported diarrhea as the only adverse reaction while those on Iron Dextran reported having headaches. Using Iron Dextran as the control, for every 17 subjects, one subject would have an adverse reaction calculated in table 3 as NNH.

Ganglui et al compared serious and non-serious adverse reactions of Iron Sucrose, Iron Dextran and Iron Gluconate. Ganglui et al listed a number of serious adverse reactions; however, the common theme of all of the serious adverse reactions were those that need immediate
attention and or resuscitation. Table 4 lists the serious adverse reactions. Of all three iron therapies, Iron Dextran had the most serious side effects compared to the other two therapies. The OR was 4.908, with a 95% CI and a p value of 0.018. The non serious adverse reactions were not statistically significant with a 95% CI. Also, the number of people that discontinued their therapy with Iron Dextran was statistically significant with a p value of 0.009 and 95% CI. Those with serious adverse reactions had anaphylactic reactions, pruritis, and hypotension. However, it should be noted that those with the serious reactions had also had previous sensitivity to other iron preparations. Fewer patients experienced serious adverse reactions such as pruritis and postural dizziness on Iron Gluconate, while non-serious reactions were mostly intestinal discomforts. The only serious adverse reaction with Iron Sucrose was hypotension. As with Iron Gluconate, the majority of non-serious adverse reactions were gastrointestinal related. Because there were three iron preparations compared in this randomized control trial, two NNH were calculated using Iron Dextran and Iron Gluconate as the control. NNH calculated were 8 and 4 respectfully.

Kosch et al found that many of the adverse effects that occurred were also common symptoms of people diagnosed with chronic kidney disease. The most common side effects were flu syndrome, infections, sinusitis and pneumonia in which the physician following the subjects ruled that these were not reactions due to the iron replacement therapy. Although Kosch et al could not relate adverse reactions to the iron preparations, more subjects dropped out of the Iron Sucrose Group than the Iron Gluconate group. For every six patients participating in the study, one person would have some sort of adverse event.

Table 3. Numbers Needed to Harm comparing Iron Gluconate, Iron Sucrose and Iron Dextran

<table>
<thead>
<tr>
<th>Author</th>
<th>RRI</th>
<th>ARI</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kosch et al</td>
<td>0.37</td>
<td>0.17</td>
<td>6</td>
</tr>
<tr>
<td>(Iron Sucrose vs. Iron Gluconate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Sav et al (Iron Sucrose vs. Iron Dextran)</td>
<td>0.16</td>
<td>0.06</td>
<td>17</td>
</tr>
<tr>
<td>Ganguli et al (Iron Sucrose vs. Iron Dextran)</td>
<td>-0.6</td>
<td>-0.12</td>
<td>8</td>
</tr>
<tr>
<td>Ganguli et al (Iron Sucrose vs. Iron Gluconate)</td>
<td>-0.47</td>
<td>-0.07</td>
<td>14</td>
</tr>
</tbody>
</table>

RRI-relative risk increase, ARI-absolute risk increase, NNH-numbers needed to harm

**Table 4. Serious Adverse Reactions listed by Ganguli et al**

<table>
<thead>
<tr>
<th>Death</th>
<th>Bradycardia</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Arrhythmias</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>Cyanosis</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Seizures</td>
<td>Seizures</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Hypotension</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

**Discussion**

Anemia is a common problem for people with CKD. However, it is known that oral preparations of iron therapy are not as effective in people with chronic kidney disease. Therefore, parenteral interventions of iron replacement therapy are necessary to correct anemia in these people. Different forms of parenteral iron therapy have caused adverse reactions in the past leading to the need to find an effective yet safe iron replacement therapy for these patients. Over all, the articles that compared Iron Sucrose to Iron Dextran observed that Iron Sucrose has led to less adverse reactions and seems to be safer without using a test dose on patients. It was also noted that subjects who had previous reactions to Iron Dextran had no reaction to Iron Sucrose.

Iron Sucrose labeled use is for people with chronic kidney disease who are affected by anemia and those on dialysis with anemia. Off labeled uses include those with anemia who are receiving chemotherapy. The latest data also shows the Iron Sucrose should be used in anyone
who has had sensitivity to Iron Dextran. The majority of the articles share the limitation of small sample size. Also, the open label study was a limitation to biases. Limitations that I ran across were the inability to compare Iron Sucrose to a placebo or Iron Sucrose to each form of iron preparations individually.

Conclusion

In comparison to Iron Dextran and Iron Gluconate, Iron Sucrose is a safe treatment for anemia associated with Chronic Kidney Disease. In the article by Kosch et al, it is concluded that although both Iron Sucrose and Iron Gluconate are effective and safe, there is a benefit to Iron Sucrose because it is a once monthly dose where as Iron Gluconate is a once weekly dose. Furthermore, Kosch et al note that this is an even greater benefit for those that are pre dialysis in that there are fewer visits needed to be made to a clinic. Another benefit for those with CKD is that previous sensitivities to Iron Dextran were not present when using Iron Sucrose. It was also observed that even those patients that had adverse reactions of some sort may not be definitively due to the iron preparation but based on numerous other health factors. It seems that the rate at which the iron preparations are given can be a player in the number of adverse reactions that are had and for those that are hypersensitive may benefit from a slower infusion rate.

Another area that is understudied is the effects of leukocytosis and its potential increased risk for associated morbidities and infection. Although at this point, this reaction has only been seen with Iron Gluconate, it is worth further investigation. As research in this area of medicine expands, it may be helpful to research randomized dosages of the iron preparations so that there aren’t as large of increases in hemoglobin, hematocrit and ferritin that is seen in some patients.
References


