INTRAVENOUS IRON SUCROSE IN PERITONEAL DIALYSIS PATIENTS WITH RENAL ANEMIA

Han Li and Shi-Xiang Wang

Blood Purification Center, Beijing Chaoyang Hospital, Capital University of Medical Sciences, Beijing, China

Objective: To explore the safety and efficacy of intravenous (IV) iron sucrose in maintenance peritoneal dialysis (PD).

Design: Randomized, controlled, parallel-group single-center trial.

Setting: Blood Purification Center of Chaoyang, Beijing Capital University of Medical Science, China.

Methods: 46 patients on PD were involved in this trial. 26 patients received IV iron sucrose (200 mg iron) once per week for 4 weeks then once every other week for a further 4 weeks. The other 20 patients received oral ferrous succinate, 200 mg three times per day, for 8 weeks. Hemoglobin, hematocrit, serum ferritin (SF) level, and transferrin saturation (TSAT) were assessed at baseline and then again after 2, 4, and 8 weeks of treatment.

Results: There were no differences between the IV and oral groups in terms of sex, age, duration of PD, mean dialysate dosage per day, erythropoietin dosage per week, or hematological parameters at baseline. After 4 and 8 weeks of treatment, mean Hb and Hct were significantly increased in the IV group and were also significantly higher than those in the oral group. Levels of SF and TSAT were also significantly increased in the IV group, and significantly higher than in the oral group. After 8 weeks, the response rate in the IV group was 94.8%, which was significantly higher than that in the oral group. The mean erythropoietin dose was significantly lower in the IV group than in the oral group. Hb, Hct, SF, and TSAT levels were maintained between 4 and 8 weeks in the IV group despite the decrease in dose frequency. There were no adverse events with IV iron. Eight patients in the oral group had adverse gastrointestinal effects.

Conclusion: IV iron sucrose is safe in PD patients. It increases Hb levels and serum iron parameters more effectively than oral iron; it is well tolerated and can permit reductions in the required dose of erythropoietin.

Renal anemia is one of the most common complications of chronic renal failure. It may have a severe impact on the quality of life of patients on maintenance peritoneal dialysis (PD) therapy (1). Use of recombinant human erythropoietin (rHuEPO) has been a milestone in renal anemia therapy and has greatly improved therapy outcome. But the efficacy of rHuEPO therapy is affected by many factors, of which iron deficiency is the most common. Although iron deficiency may be corrected by oral iron supplementation in some patients, supplementation is often limited by poor compliance and adverse gastrointestinal reactions. Intravenous (IV) iron can reduce the occurrence of adverse gastrointestinal reactions and overcomes the problem of compliance with oral treatment (2). Intravenous iron preparations commonly used in Western countries include iron sucrose, sodium ferric gluconate, and iron dextran. They are similar in the amount of iron they deliver and the degree to which they can improve anemia, but they have different safety profiles and adverse reaction risks. Iron sucrose is safer than iron dextran, is generally considered a safe IV iron preparation (3–5), but is seldom used in patients on PD in China. Even when iron sucrose is used in China, there are no clear guidelines on dosage or frequency of administration. This study was therefore designed to compare the clinical outcomes and safety of IV iron sucrose and oral ferrous succinate in combination with rHuEPO therapy in patients on maintenance PD.

METHODS

PARTICIPANTS

Patients were recruited from the Blood Purification Center, Chaoyang Hospital, Beijing Capital University of Medical Science, China.
Patients were included in the study if they were on maintenance PD (daily dose 6 – 8 L), their condition had been stable for at least 1 month, and they had serum ferritin (SF) level <500 ng/mL, transferrin saturation (TSAT) <30%, hemoglobin 60 – 90 g/L, and hematocrit of 18% – 27%.

Patients were excluded from the study if they had severe liver disease, hypersplenism, acute or chronic hemorrhage, or active ulcer; had received a blood transfusion in the previous month; had severe inflammation or infection, or malignant tumors; were severely malnourished or sensitive to iron preparations, or had serum high-sensitivity C-reactive protein (hs-CRP) level ≥20 mg/L.

Iron treatment was stopped in patients if they had SF ≥800 ng/mL and/or TSAT ≥50%.

Participants were withdrawn from the trial if they required a blood transfusion, had a severe infection, heart failure, or severe malnutrition, or were unable to follow the trial protocol.

Participants were randomly assigned by computer-generated random number list to receive either IV (IV group) or oral (oral group) iron.

TREATMENTS

The IV group received 200 mg iron sucrose (Venofer; Vifor International, St. Gallen, Switzerland) diluted in 100 mL physiological saline, infused IV for at least 30 minutes, once every week for the first 4 weeks then once every other week afterward. At the start of the study, a test dose of 25 mL was given at a rate of 1 mL/minute, and participants were closely observed for any adverse reactions. If no adverse reaction occurred, the remaining 75 mL was infused at a rate of 3 mL/minute. Treatment was given for 8 weeks.

The oral group received ferrous succinate 200 mg three times daily, taken without food when possible, for 8 weeks.

Other routine drugs, including folic acid (5 mg, 3 times daily) and vitamin B₁₂ (500 µg, every day), were continued during the trial. All patients received EPO (Shenyang Sansheng Pharmaceutical, Shenyang, China) at a dose of 100 – 150 IU/kg/week (depending on previous treatment) during the study. EPO dose titration was allowed at 2, 4, and 8 weeks after the treatment. If Hb reached 110 g/L, the EPO dose was decreased by 25%.

ASSESSMENTS

Blood samples were taken at baseline then after 2, 4, and 8 weeks of treatment, and Hb, Hct, reticulocytes, SF, and TSAT were assessed. Hematological parameters for the IV group were assessed at least 1 week after the last dose of IV iron, according to the NKF-KDOQI guidelines. White blood cell count (WBC) and serum levels of creatinine, blood urea nitrogen (BUN), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, indirect bilirubin, intact parathyroid hormone (iPTH), hs-CRP, folic acid, vitamin B₁₂, potassium, sodium, and chloride were measured before and after treatment.

Any reactions such as gastrointestinal symptoms, flushing, palpitation, or hypersensitivity were recorded.

OUTCOME CRITERIA

Response was defined as Hb increase >15 g/L or Hct increase >5%. Response rate (%) was defined as (responses/total cases) ×100.

STATISTICAL METHODS

The SPSS 11.5 (SPSS Inc., Chicago, Illinois, USA) statistical package was used. Data are shown as mean ± standard error. Comparisons were performed using t-test or chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

Forty-six patients on maintenance PD (21 males, 25 females) were recruited to the study. They had a mean age of 57.9 ± 15.5 years (range 23 – 83 years) and mean dialysis history of 7.2 ± 5.6 months (range 3 – 40 months). History of anemia was 16.1 ± 5.8 months (range 6 – 26 months). Duration of EPO use before this study was 5.1 ± 3.1 months (range 2 – 12 months). Patients were not given any iron supplementation for at least 1 month before the study. Reasons for dialysis were diabetic renal disease (22 patients), chronic interstitial nephritis (7 patients), chronic nephritis (4 patients), hypertensive renal disease (4 patients), polycystic kidney (1 patient), and unidentified (8 patients). Patients were randomly grouped into the IV group (n = 26) or the oral group (n = 20). No patient withdrew from the trial during the study period. There were no significant differences between the two groups in terms of age, sex ratio, duration of dialysis, daily dialysate dosage, EPO dosage, Hb, Hct, SF, TSAT, or serum levels of iPTH, hs-CRP, creatinine, BUN, folic acid, or vitamin B₁₂ at baseline (see Table 1).

Hemoglobin and Hct increased significantly at 2 weeks of therapy in the IV group compared with baseline. He-
moglobin and Hct increased significantly after 4 and 8 weeks of therapy in both the IV and the oral groups, but the increases in the IV group were significantly greater than those in the oral group after 4 weeks and were maintained after this point. Mean reticulocyte count in the IV group was significantly increased at 2 weeks and was greater than that of the oral group, but was not significantly different from the reticulocyte counts at 4 weeks and 8 weeks. Mean reticulocyte counts in the oral group were significantly increased at 4 weeks, and were not significantly different from the reticulocyte counts at 2 weeks and 8 weeks. After 8 weeks of iron supplementation, mean EPO dose in the IV group was significantly lower than in the oral group (see Table 2). The total response rate at 8 weeks was 94.8% for the IV group, which was significantly higher than that of the oral group (55.0%) (see Table 3).

There were no significant differences in SF levels and TSAT between the two groups at baseline. Serum ferritin levels and TSAT increased significantly in both groups at 4 and 8 weeks. The increase in the IV group was significantly higher than that in the oral group. No patients had SF >800 ng/mL or TSAT >50% at any time point. During the maintenance phase, SF levels and TSAT at 8 weeks showed no significant difference compared to those at 4 weeks (see Table 2).

After 8 weeks, there were no significant differences between the two groups in WBC counts or serum levels of creatinine, BUN, albumin, ALT, AST, direct bilirubin, indirect bilirubin, iPTH, hs-CRP, folic acid, vitamin B\textsubscript{12}, K, Na, or Cl (see Table 4).

**ADVERSE EVENTS**

Vital signs in the two groups were stable during the study. There were no adverse events in the IV iron group. In the oral group, 8 patients (40%) reported gastrointestinal symptoms. No patients withdrew from the study.

**DISCUSSION**

Renal anemia is a common and important complication of chronic renal failure. It can result in many physiological abnormalities such as decreased tissue oxygen supply and utilization (7), ventricular hypertrophy and heart failure (8,9), and immunosuppression (10) and can also adversely affect patient quality of life. Effective treatment of anemia has been shown to significantly improve the quality of life of patients on dialysis (1,11). Anemia commonly occurs in patients with chronic renal failure, resulting from insufficient synthesis of EPO by the body. rHuEPO therapy is therefore ideal for such patients and can produce a significant effect. However, use of rHuEPO increases iron demands. Although iron storage may be normal or even increased in some, many patients lack available iron since stored iron cannot be effectively released to meet the demands of the bone marrow for hematopoiesis. This may cause functional iron deficiency and may reduce the efficacy of anemia therapies (12).

Although oral iron administration is the primary treatment for iron deficiency, it has many disadvantages, such as poor iron absorption and adverse gastrointestinal reactions, that often lead to poor compliance. However, the use of IV iron reduces the risk of adverse gastrointestinal reactions and overcomes the problem of poor compliance with oral therapy (13,14). Another advantage of the IV route is that the iron will not be eliminated by first-pass effects or by high efficiency dialysis membranes, and the iron can be quickly released into the reticuloendothelial system and used for erythropoiesis, thus increasing its bioavailability.

In the present study, serum iron parameters were all significantly improved in the IV group, with a significant increase in parameters indicating iron storage and...
The effect was significantly greater with IV iron than with oral iron. Not only were the increases in Hb and Hct significantly higher at 4 weeks and 8 weeks, but also the dosage of EPO was significantly lower at 8 weeks in the IV group than in the oral group. This suggests that IV infusion of iron sucrose can effectively correct iron deficiency in patients on PD and decrease the required dose of rHuEPO.

The aim of iron supplementation is to increase red blood cell (RBC) production without increasing TSAT and/or SF beyond target levels (15). Results from this study show that Hb and Hct increased significantly in patients on PD after 4 weeks of IV iron supplement at a dose of 200 mg once per week. Furthermore, Hb, Hct, and RBC levels at 8 weeks were not significantly different from those at 4 weeks in the IV group. Hemoglobin and Hct reached targeted values in 94.8% of patients in this study.

We gave weekly doses of 200 mg iron for the first 4 weeks, then 200 mg every other week for 8 weeks. This dosing frequency appears to maintain the iron parameters and Hb and Hct levels in most patients on PD. Currently, there is no recommended dosing frequency for iron during the maintenance phase (12). We suggest that once the targets TSAT £ 50% and SF £ 800 ng/mL have been achieved (15), therapy can be switched to a maintenance dose of 200 mg every other week.

Iron parameters should be monitored in all patients receiving IV iron to keep TSAT £ 50% and SF £ 800 ng/mL (15).

### TABLE 2
Hematologic Parameters and Measurements of Iron Metabolism Before and After Intravenous (IV) or Oral Iron Supplementation

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>At 2 weeks</th>
<th>At 4 weeks</th>
<th>At 8 weeks</th>
<th>Increase at 8 weeks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>88.3±8.3</td>
<td>99.1±4.7c,d</td>
<td>117.3±11.5c,d</td>
<td>122.1±10.5c,d</td>
<td>34.1±16.5d</td>
</tr>
<tr>
<td>Oral</td>
<td>88.6±8.8</td>
<td>92.3±5.4</td>
<td>99.5±11.6c</td>
<td>106.3±10.4c</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>24.2±2.3</td>
<td>29.8±3.2c,d</td>
<td>34.6±2.8c,d</td>
<td>35.3±2.5c,d</td>
<td>36.1±10.7d</td>
</tr>
<tr>
<td>Oral</td>
<td>24.1±2.8</td>
<td>25.3±3.3</td>
<td>27.6±2.9c</td>
<td>30.5±2.4c</td>
<td>16.4±10.8</td>
</tr>
<tr>
<td>IV</td>
<td>1.4±0.6</td>
<td>1.7±0.6c</td>
<td>1.4±0.5</td>
<td>1.4±0.4</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>1.4±0.7</td>
<td>1.3±0.7</td>
<td>1.6±0.4c</td>
<td>1.4±0.3</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>7576±1032</td>
<td>7576±1032</td>
<td>7576±1032</td>
<td>6100±1043c,d</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>7635±1024</td>
<td>7635±1024</td>
<td>7635±1024</td>
<td>7635±1024</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>110.6±54.1</td>
<td>216.4±56.1c,d</td>
<td>465.8±65.2c,d</td>
<td>466.7±85.3c,d</td>
<td>326.8±80.1d</td>
</tr>
<tr>
<td>Oral</td>
<td>111.2±54.8</td>
<td>185.3±56.6</td>
<td>248.3±75.1c</td>
<td>299.4±83.2c</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>19.4±8.8</td>
<td>28.8±15.2c</td>
<td>36.8±15.4c</td>
<td>37.8±16.1c,d</td>
<td>93.9±26.7d</td>
</tr>
<tr>
<td>Oral</td>
<td>19.3±8.1</td>
<td>21.6±16.1</td>
<td>25.8±17.3c</td>
<td>25.7±17.5c</td>
<td></td>
</tr>
</tbody>
</table>

EPO = erythropoietin; TSAT = transferrin saturation.

- The IV group received 200 mg iron sucrose IV once every week for the first 4 weeks, then once every other week for 8 weeks.
- The oral group received ferrous succinate 200 mg, three times daily, taken without food when possible, for 8 weeks.
- Significant change from baseline (p < 0.05).
- Significant difference between IV and oral groups (p < 0.05).

### TABLE 3
Response Rates

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Full response (%)</th>
<th>Partial response (%)</th>
<th>Minimal response (%)</th>
<th>Ineffective (%)</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>26</td>
<td>20 (83.3)</td>
<td>3 (11.5)</td>
<td>3 (11.5)</td>
<td>0</td>
<td>94.8d</td>
</tr>
<tr>
<td>Oral</td>
<td>20</td>
<td>6 (30.0)</td>
<td>5 (25.0)</td>
<td>9 (45.0)</td>
<td>0</td>
<td>55.0</td>
</tr>
</tbody>
</table>

IV = intravenous.

- Full response: Hb ≥30 g/L or Hct ≥10% after or during therapy, or Hb concentration reaching 110 g/L, Hct reaching 33%; Partial response: Hb increase ≥15 g/L but <30 g/L after therapy, or Hct ≥5% but <10%; Minimal response: Hb or Hct increased after therapy, but the increase of Hb <15 g/L or the increase in Hct <5%.
- The IV group received 200 mg iron sucrose IV once every week for the first 4 weeks, then once every other week for 8 weeks.
- The oral group received ferrous succinate 200 mg, three times daily, taken without food when possible, for 8 weeks.
- Significant difference between groups (p < 0.05).
Many factors should be considered in the selection of iron preparations. Adverse gastrointestinal reactions, such as nausea, vomiting, abdominal pain, constipation, and diarrhea, often occur with oral iron therapy and may affect patient compliance. And IV iron supplementation has been associated with vascular reactions and low blood pressure (16). Therefore, possible adverse reactions should be considered before switching to IV iron preparations. However, much experience of adverse reactions came from the use of iron dextran rather than iron sucrose. Severe or even life-threatening adverse reactions, including hypersensitive shock (incidence rate 0.7%), can occur with iron dextran (17,18). Chertow et al.’s research (19) showed that the absolute rates of life-threatening adverse drug events 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. Other adverse reactions include myalgia, arthralgia, flushing, back pain, abdominal pain, and diarrhea. More-recent studies suggest that the incidence of adverse reactions with iron sucrose and sodium ferric gluconate is significantly lower than with iron dextran, and that severe adverse reactions are rare (15). In the present study, no severe adverse reactions such as hypersensitivity or hypersensitive shock occurred in the IV group, nor were there any adverse gastrointestinal reactions. Therefore, our findings suggest that, for patients that cannot tolerate oral iron or that have a poor response to oral iron therapy, iron sucrose is a safe and effective choice.

It has been suggested in recent years that IV iron supplementation may worsen the microinflammatory state and oxidative stress (20). High-sensitivity CRP is a sensitive parameter for detecting the chronic inflammatory state in patients on PD. In the present study we found that hs-CRP was not increased following iron sucrose administration, indicating that IV iron supplementation did not worsen the inflammatory state. This may possibly be explained by the low dose of iron sucrose, the slow infusion rate, and the low drug concentration, which would not be expected to produce free iron after infusion and therefore should not exacerbate oxidative stress. However, this needs confirmation by further studies.

We conclude that iron deficiency is relatively common in patients receiving PD. Oral iron supplementation has many adverse reactions and cannot meet the demand for erythropoiesis. Use of IV iron sucrose can effectively correct iron deficiency, increase iron storage, decrease the required dose of rHuEPO, and improve anemia in patients on PD. Intravenous iron sucrose also has a low incidence of adverse reactions. It is now clear that the administration frequency of infusing IV iron sucrose 200 mg twice per week is appropriate to most PD patients in the maintenance phase. However, this needs confirmation by

### Table 4
Other Laboratory Hematologic Parameters Before and After Iron Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV group Baseline</th>
<th>IV group After 8 weeks</th>
<th>Oral group Baseline</th>
<th>Oral group After 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>980.8±275.5</td>
<td>982.3±265.4</td>
<td>982.6±273.3</td>
<td>981.2±265.5</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>20.6±6.3</td>
<td>20.4±6.8</td>
<td>20.5±7.0</td>
<td>20.1±7.2</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.7±3.2</td>
<td>38.0±2.9</td>
<td>37.6±2.6</td>
<td>37.7±3.5</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>18.1±6.8</td>
<td>18.3±6.2</td>
<td>17.9±9.0</td>
<td>17.8±8.8</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>29.1±6.0</td>
<td>28.9±5.9</td>
<td>28.6±8.4</td>
<td>28.7±6.7</td>
</tr>
<tr>
<td>Direct bilirubin (µmol/L)</td>
<td>1.6±1.2</td>
<td>1.7±1.3</td>
<td>1.5±1.2</td>
<td>1.6±1.4</td>
</tr>
<tr>
<td>Indirect bilirubin (µmol/L)</td>
<td>10.8±6.5</td>
<td>11.1±4.9</td>
<td>11.0±5.4</td>
<td>11.4±5.7</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>4.1±2.4</td>
<td>4.3±3.1</td>
<td>4.2±2.7</td>
<td>4.3±3.0</td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>140.3±10.1</td>
<td>140.5±11.1</td>
<td>141.1±10.6</td>
<td>141.2±10.8</td>
</tr>
<tr>
<td>Cl (mmol/L)</td>
<td>100.1±11.8</td>
<td>101.2±11.9</td>
<td>100.6±11.9</td>
<td>100.4±11.3</td>
</tr>
<tr>
<td>iPTH (ng/mL)</td>
<td>228.7±54.5</td>
<td>229.4±51.4</td>
<td>229.4±59.6</td>
<td>230.4±52.3</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>1.7±1.2</td>
<td>1.7±1.4</td>
<td>1.8±1.1</td>
<td>1.8±1.3</td>
</tr>
<tr>
<td>Folic acid (µg/L)</td>
<td>15.9±7.3</td>
<td>16.0±6.9</td>
<td>16.1±7.2</td>
<td>15.9±6.3</td>
</tr>
<tr>
<td>Vitamin B₁₂ (ng/L)</td>
<td>748.2±397.4</td>
<td>749.7±395.5</td>
<td>750.2±417.8</td>
<td>749.9±413.2</td>
</tr>
<tr>
<td>WBC (×10⁹/L)</td>
<td>6.4±2.4</td>
<td>6.3±2.0</td>
<td>6.3±3.1</td>
<td>6.3±2.8</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; iPTH = intact parathyroid hormone; hs-CRP = high-sensitivity C-reactive protein; WBC = white blood cell count; IV = intravenous.

a The IV group received 200 mg iron sucrose IV once every week for the first 4 weeks, then once every other week for 8 weeks.
b The oral group received ferrous succinate 200 mg, three times daily, taken without food when possible, for 8 weeks.
further longer-term follow-up of the use of intravenous iron preparation in peritoneal dialysis patients.

REFERENCES