Intravenous versus oral iron for treatment of iron deficiency in non-hemodialysis-dependent patients with chronic kidney disease

ANNE MARIE LILES

A nemia develops in the early stages of chronic kidney disease (CKD), primarily due to the progressive decrease in erythropoietin production by the kidneys. Even at stage 1 or 2 CKD, 25% of patients have hemoglobin levels of ≤12 g/dL. Although erythropoiesis-stimulating agents (ESAs) are the mainstay of anemia treatment, concomitant iron supplementation is often required. Patients with CKD are at risk for developing iron deficiency due to frequent blood testing, decreased dietary intake, inflammation, decreased gastrointestinal absorption, the use of phosphate binders, hemodialysis, and treatment with ESAs. Patients with CKD are at risk for developing iron deficiency due to frequent blood testing, decreased dietary intake, inflammation, decreased gastrointestinal absorption, the use of phosphate binders, hemodialysis, and treatment with ESAs. Seven randomized, controlled trials compared i.v. and oral iron in this population, six in patients treated with ESAs and one in patients not receiving ESAs. Two studies found no difference between i.v. and oral iron. An additional study found the two formulations to be equivalent when evaluating ESA dosage requirements. All studies found i.v. iron to be superior in increasing ferritin and transferrin saturation (TSAT) levels. Five of the studies compared baseline laboratory values for patients treated with i.v. and oral iron; all of these found oral iron to significantly increase hemoglobin, ferritin, or TSAT levels. Only one trial found a significant decrease from baseline in ferritin and TSAT for oral iron. Interpretation of the results of these studies is limited by several factors, the most significant of which is a short study duration, ranging from 21 days to six months.

Conclusion. Published evidence does not support the use of i.v. iron over oral iron to treat deficiencies in non-hemodialysis-dependent patients with CKD. While studies found that i.v. iron significantly increased serum levels of ferritin and TSAT, hemoglobin levels were not consistently raised.

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NKF has not issued a guideline for the type of iron supplementation to use in ND-CKD patients.1 Guidelines issued by the European Renal Association and European Dialysis and Transplant Association recommend i.v. iron for patients with CKD, regardless of the use of hemodialysis, due to the poor absorption of oral iron in these patients.6 Evidence demonstrates the superiority of i.v. iron in hemodialysis patients.7,8 In contrast, evidence evaluating the efficacy of i.v. versus oral iron in ND-CKD patients is unclear. Both dosage forms have disadvantages that may influence the health care practitioner’s choice of iron. Oral iron has been associated with adverse gastrointestinal effects and may require the administration of multiple doses daily.3 Absorption of oral iron may also be limited by decreased gastrointestinal absorption due to the inflammation associated with CKD. This inflammation increases the production of hepcidin, a protein produced in the liver that regulates iron homeostasis, thereby inhibiting the absorption of iron from the intestine and inhibiting iron release from macrophages and hepatocytes.9 The use of i.v. iron is more costly than oral iron when accounting for drug cost, administration costs, and indirect costs to the patient for time and travel and can cause rare but serious short-term effects including anaphylactic-type reactions, hypotension, and arthralgia. The frequency of these reactions varies among i.v. iron products and is highest with high-molecular-weight products, which have also been associated with long-term effects such as infection, atherosclerosis, endothelial dysfunction, and renal injury (transient proteinuria and tubular damage).10

Intravenous versus oral iron

Stoves et al. The first prospective, randomized controlled trial comparing i.v. and oral iron in ND-CKD patients was conducted by Stoves et al.11 in 2001. Forty-five anemic patients (hemoglobin concentration of <11.0 g/dL) were treated for an average of 5.2 months with either 200 mg oral ferrous sulfate three times daily (n = 23) or 300 mg i.v. iron sucrose once monthly (n = 22). Erythropoietin was also initiated at a dosage of 2000 units two times a week and then adjusted based on hemoglobin response. Baseline data were similar between groups for mean hemoglobin, ferritin, and hypochromia.

Mean ESA dosage requirements did not significantly differ between the i.v. and oral iron groups (41.6 and 33.5 units/kg/week, respectively), nor did mean final hemoglobin concentrations (12.5 and 12.2 g/dL, respectively). While mean ferritin concentrations were significantly higher in the i.v. group (330 ng/mL versus 95 ng/mL), there was no significant difference in the frequency of red cell hypochromia, which Stoves et al. suggested is a more direct measure of iron supply for erythropoiesis.

Five patients (55%) in the oral iron group had diabetes, compared with none in the i.v. group, which may have confounded the results as diabetes is associated with greater inflammation and the potential for decreased iron absorption.12 In addition, the number of patients being treated with angiotensin-converting enzyme inhibitors and angiotensin-receptor antagonists was higher in the oral iron group, potentially confounding the results due to potential drug interaction with ESAs. This drug interaction is proposed to be a result of the association of the renin-angiotensin system with endogenous erythropoietin production and results in the subsequent blunting of response to the ESA.13-15 The rate of adverse gastrointestinal effects was higher in the oral iron group; however, no details regarding specifics of these adverse effects were given, only that they were of mild severity. Statistical test results were not specifically reported in this study, only statements as to whether a difference was statistically significant. The investigators concluded that monthly 300-mg doses of i.v. iron sucrose were not superior to 200-mg doses of oral ferrous sulfate administered three times daily with regard to hemoglobin response and ESA dosage requirements.

Aggarwal et al. A subsequent study comparing i.v. and oral iron in ND-CKD patients was published by Aggarwal et al.16 in 2003. Forty patients were randomized to receive either oral ferrous sulfate 200 mg three times daily (n = 20) or i.v. iron dextran 200 mg two times a month (n = 20) for a duration of three months. In addition, erythropoietin was initiated in all patients at a dosage of 2000 units two times a week. Unlike the study by Stoves et al.,11 this dosage was not adjusted during the study. Baseline hemoglobin values were well below the KDOQI goal of 11–12 g/dL.1 (6.26 ± 1.0 g/dL for the oral ferrous sulfate group and 5.83 ± 0.6 g/dL for the i.v. iron dextran group). Baseline ferritin concentrations (190.27 ± 33.23 ng/mL in patients receiving oral iron and 181.44 ± 45.33 ng/mL in the group receiving i.v. iron) and TSAT (63.56% ± 11.10% and 59.78% ± 10.36%, respectively) levels were above the KDOQI’s recommended goals for ferritin (>100 ng/mL) and TSAT (>20%).1 After three months of treatment, hemoglobin levels in both groups increased from baseline; however, the i.v. iron group had a significantly higher mean hemoglobin concentration at three months.
compared with the oral iron group (10.05 ± 0.9 g/dL versus 8.94 ± 1.17 g/dL, p < 0.001). The i.v. iron group also had significant increases in TSAT and ferritin levels (p < 0.01 and p < 0.001, respectively), while the oral iron group had significant decreases in these values (p < 0.001 for both values). The authors hypothesized that the use of oral iron could eventually result in a negative iron balance and a subsequent decrease in hemoglobin levels, concluding that i.v. iron was a better choice than oral iron in ND-CKD patients treated with an ESA. No patients in either group developed noteworthy adverse effects; the number of patients experiencing gastrointestinal complications was not given. The external validity of this study is limited by the participants’ uncharacteristically low baseline hemoglobin values. In addition, because patients were iron replete at baseline, it is likely that the increases in hemoglobin resulted from the administration of the ESA rather than iron.

Charytan et al. A similar Phase II/III open-label trial conducted by Charytan et al.17 randomized 96 ND-CKD patients to receive either oral ferrous sulfate 325 mg three times daily (n = 48) or i.v. iron sucrose 200 mg every 7 days for a total of five doses (n = 48). Like the 2003 Aggarwal et al. study, erythropoietin 2000 units weekly was initiated, with no changes in the dosage during the study. Patients with hemoglobin concentrations of <10.5 g/dL, TSAT levels of <25%, and ferritin concentrations of <300 ng/mL were included in the study. The treatment duration was 29 days with final outcomes measured on day 43, two weeks after the last dose of either oral or i.v. iron. Both i.v. and oral iron groups had a significant mean increase in hemoglobin from baseline to day 43 (0.7 g/dL [p < 0.0001] and 1.0 g/dL [p < 0.0001], respectively); however, the difference between the groups was not significant. There was a significant difference in the change from baseline in ferritin levels between groups (a mean decrease of 5.1 ng/mL in the oral iron group versus a mean increase of 288.0 ng/mL for the i.v. iron group, p < 0.0001). In addition, the i.v. iron group had a mean increase of 4.5% in TSAT levels from baseline (p < 0.0001), while the oral iron group had an increase of only 0.5% (p = 0.567). The frequency of gastrointestinal symptoms was greater in the oral iron group than the i.v. group (constipation, 35.4% versus 12.5%; nausea, 10.4% versus 4.2%; vomiting, 8.3% versus 0%; and diarrhea, 8.4% versus 0%). Taste disturbances were more common in the i.v. iron group. No patients experienced serious adverse effects, including anaphylactic-type reactions. The investigators concluded that both i.v. and oral iron resulted in similar hemoglobin responses but that the lack of significant change in iron stores (TSAT levels) with oral iron may lead to an eventual loss of response to ESA therapy.

Van Wyck et al. A Phase III trial conducted by Van Wyck et al.18 attempted to control for ESAs as a confounder by limiting study inclusion to ND-CKD patients who were receiving a stable dosage of an ESA for at least eight weeks or who had not been treated with an ESA. Patients’ ESA dosages were maintained throughout the duration of the trial. A total of 188 patients were randomized to receive either 325 mg oral ferrous sulfate three times daily for 56 days (n = 93) or 1000 mg i.v. iron sucrose in divided doses over 14 days (n = 95). Other inclusion criteria included a hemoglobin concentration of ≤11.0 g/dL, a TSAT level of ≤25%, and a ferritin concentration of ≤300 ng/mL. A greater percentage of patients in the i.v. iron group achieved an increase of ≥1.0 g/dL in hemoglobin concentration compared with the oral iron group (44.3% [n = 35] versus 28.0% [n = 23], p = 0.0344). Ferritin and TSAT values increased significantly from baseline in both groups, but the increase in ferritin in the i.v. iron group was significantly greater than that in the oral group. More patients in the i.v. iron group reported nonserious adverse effects than in the oral iron group (22% [n = 20] versus 19% [n = 17], respectively). Taste disturbances were the most common gastrointestinal complaint with i.v. iron, and constipation, diarrhea, nausea, vomiting, and dyspepsia were the most common adverse effects reported in patients treated with oral iron. Three patients were reported to have experienced symptomatic hypotension with i.v. iron. The investigators concluded that 1000 mg i.v. iron sucrose administered in divided doses was superior to 325 mg oral ferrous sulfate given three times daily in ND-CKD patients with anemia and iron deficiency.

Spinowitz et al. A Phase III trial by Spinowitz et al.19 randomized 304 ND-CKD patients to receive 200 mg oral ferrous fumarate daily for 21 days (n = 76) or two 510-mg doses of i.v. ferumoxytol within 2–8 days (n = 228). Similar to the study conducted by Van Wyck et al., patients were included only if they were receiving a stable ESA dosage or not taking an ESA. ESA dosages were not changed and new regimes of ESAs were not initiated during the study. Both groups had a mean hemoglobin concentration of 9.96 g/dL, a mean ferritin concentration of >100 ng/mL at baseline, and a mean TSAT level of <20%. Final outcomes were measured on day 35, two weeks after the last dose of oral iron was administered. The mean increase in hemoglobin concentration from baseline was greater in the i.v. group (0.82 ± 1.24 g/dL versus 0.16 ± 1.02 g/dL, p < 0.0001). Increases in ferritin concentrations and TSAT levels were also greater in the i.v. group (mean ferritin increase, 381.7 ng/mL versus 6.9 ng/mL, p < 0.0001; mean TSAT increase, 9.8% versus 1.3%,...
Treatment-related adverse effects occurred more frequently in the oral iron group (24.0% [n = 18] versus 10.6% [n = 23]). Constipation and vomiting were most frequently reported with oral iron. The investigators concluded that i.v. ferumoxytol was more effective than oral ferrous fumarate in increasing hemoglobin levels in ND-CKD patients.

Qunibi et al. The most recent trial comparing i.v. and oral iron in ND-CKD patients was conducted by Qunibi et al.20 This Phase III trial included patients with hemoglobin concentrations of ≤11.0 g/dL, TSAT levels of ≤25%, and ferritin concentrations of ≤300 ng/mL. A total of 255 patients were randomized to receive oral ferrous sulfate 325 mg three times daily for 56 days (n = 103) or 500–1000 mg of i.v. ferric carboxymaltose (n = 152). The initial dose of i.v. ferric carboxymaltose was 1000 mg, and 500-mg doses were subsequently administered on day 17 and again on day 31 if a patient’s TSAT level remained at <30% and the ferritin concentration was <300 ng/mL, for a maximum of two additional doses. Forty-two percent of patients received more than one dose of i.v. ferric carboxymaltose. Mean increases in ferritin and TSAT values from baseline to day 56 were greater in the i.v. iron group (ferritin, 358.8 ± 178.4 ng/mL versus 25.8 ± 49.4 ng/mL, p < 0.001; TSAT, 12.1% ± 8.8% versus 7.0% ± 10.3%, p < 0.001). However, ferritin concentrations in the i.v. group did show significantly greater mean increases than the oral group on day 14 after the administration of only 1000 mg of i.v. iron (p < 0.001). Hemoglobin changes were also significantly greater in the i.v. group (1.05 ± 1.10 g/dL versus 0.70 ± 1.25 g/dL, p = 0.034).

It should also be noted that the levels of iron stores used to determine the need for additional i.v. iron doses were greater than the recommended goals. In clinical practice, it is uncommon for patients to receive >1 g of i.v. iron in a 30-day period, while oral iron is typically dosed at a maximum of 200 mg elemental iron daily (ferrous sulfate 325 mg three times daily contains 195 mg of elemental iron). Constipation was the only adverse effect whose frequency significantly differed between groups (17.5% with oral iron versus 1.4% with i.v. iron, p < 0.001). The authors concluded that i.v. ferric carboxymaltose was more effective and better tolerated than oral ferrous sulfate for the treatment of iron deficiency in ND-CKD patients. However, given the disparity in dosing, the 0.35-g/dL difference in mean hemoglobin concentrations may not be clinically significant.

**Oral versus i.v. iron in patients not receiving ESAs**

A study conducted by Agarwal et al.21 is the only published trial to compare i.v. and oral iron solely in ND-CKD patients not receiving an ESA. Seventy-five patients were randomized to receive oral ferrous sulfate 325 mg three times daily for six weeks (n = 39) or i.v. sodium ferric gluconate 250 mg weekly for four doses (n = 36). Baseline data were similar between groups and below the KDOQI's recommended goals for hemoglobin, TSAT, and ferritin values. The mean change in hemoglobin concentration from baseline did not significantly differ between treatment groups (0.4 ± 0.8 g/dL versus 0.2 ± 0.9 g/dL for the i.v. and oral iron groups, respectively). The mean change in TSAT level from baseline significantly differed between the i.v. and oral iron groups (mean increase of 8.3% ± 7.5% versus 2.9% ± 8.8%, respectively; p = 0.007). Similarly, increases in ferritin concentrations significantly differed between the i.v. and oral iron groups (mean increase of 232.0 ± 160.8 ng/mL versus 55.9 ± 236.2 ng/mL, p < 0.001). The increases in TSAT and ferritin values in both groups were also noteworthy when compared with their respective baseline values. A greater number of patients in the i.v. iron group experienced adverse effects (29.5% versus 20% in the oral iron group). Constipation was most frequent in the oral iron group, and hypotension and nausea were the most frequent adverse effects in the i.v. iron group. Three of the adverse events in the i.v. iron group were classified as serious. The authors concluded that oral and i.v. iron resulted in similar increases in hemoglobin concentrations in iron-deficient ND-CKD patients not receiving an ESA.

**Discussion**

Interpretation of the results of these studies is limited by several factors, the most significant of which is short study duration, ranging from 21 days to six months. ND-CKD patients, especially those receiving ESAs, will likely require long-term treatment with oral iron or periodic i.v. iron infusions throughout the course of the disease. Increases in hemoglobin values after oral iron intake are typically seen in four to eight weeks; however, repletion of iron stores generally requires an additional three to six months or longer.22 Despite three studies that found no significant difference in hemoglobin values with i.v. and oral iron therapy, all found a significantly greater increase in ferritin or TSAT with i.v. iron.11,17,21 It is unknown whether this difference would persist if patients were treated with oral iron for a longer duration. Two studies that found i.v. iron to be superior did report significant increases in hemoglobin values from baseline with oral iron16,18; however, it is unknown if long-term treatment would eventually result in a negative iron balance and thus a decrease in hemoglobin concentration.

While adverse effects were reported, the short duration of the studies limited the ability to evaluate long-term effects. Studies showing increased oxidative stress with the
use of i.v. iron have suggested that repeated treatment with i.v. iron may lead to atherosclerosis, endothelial dysfunction, and renal injury.\textsuperscript{23,24} These studies have identified biomarkers of oxidative stress but have not evaluated clinical outcomes. Long-term effects of i.v. versus oral iron cannot be evaluated from the studies reviewed.

Most of the trials included patients receiving treatment with an ESA. While some investigators tried to control for this by including only patients on stable dosages, this confounder makes it difficult to see the true effect of iron on hemoglobin and iron laboratory values. It is possible that in studies finding increases in hemoglobin values but either no change or decreases in iron stores with oral iron, the effect may have been due to the ESA. However, the inclusion of patients treated with ESAs is more reflective of actual clinical practice with the ND-CKD population. In the only trial comparing ESA dosage requirements in ND-CKD patients treated with oral or i.v. iron, Stoves et al.\textsuperscript{11} found no difference in hemoglobin values between the groups, supporting the two additional trials that found no significant difference in hemoglobin concentrations between oral and i.v. iron groups\textsuperscript{17,21}; however, there are no trials confirming or refuting these data.

The argument could be made that because i.v. iron has consistently been associated with improvements in serum iron markers, it is superior to oral iron. However, a recently published study by Ferrari et al.\textsuperscript{25} questioned the utility of serum iron markers in guiding iron repletion in ND-CKD patients. When comparing serum iron laboratory values (TSAT and ferritin) to liver iron concentration in ND-CKD patients after the administration of a single high dose of i.v. iron, only liver iron concentration had a consistent dose-dependent response. The results suggest that increases in iron in the body may not be reflected in traditional serum iron laboratory values. Therefore, when reviewing the data comparing oral and i.v. iron, it appears that the serum hemoglobin value is a better indicator of treatment efficacy deficiency.

Small study populations also make it difficult to rule out a possible Type II error. In 2008, Rozen-Zvi et al.\textsuperscript{26} conducted a meta-analysis that included six studies reviewed herein. The authors found a significantly greater increase in hemoglobin concentration with i.v. iron versus oral iron (weighted mean difference, 0.31 g/dL; 95% confidence interval, 0.09–0.53), but this small difference could be viewed as clinically insignificant.

**Conclusion**

Published evidence does not support the use of i.v. iron over oral iron to treat deficiencies in ND-CKD patients. While studies have found that i.v. iron significantly increased serum levels of ferritin and TSAT, hemoglobin levels were not consistently raised.

**References**


