CLINICAL RESEARCH STUDY

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The Comparative Short-term Effectiveness of Iron Dosing and Formulations in US Hemodialysis Patients

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ABSTRACT

BACKGROUND: Intravenous iron is used widely in hemodialysis, yet there are limited data on the effectiveness of contemporary dosing strategies or formulation type.

METHODS: We conducted a retrospective cohort study using data from the clinical database of a large dialysis provider (years 2004-2008) merged with administrative data from the US Renal Data System to compare the effects of intravenous iron use on anemia management. Dosing comparisons were bolus (consecutive doses $\geq$100 mg exceeding 600 mg during 1 month) versus maintenance (all other iron doses during the month); and high (>200 mg over 1 month) versus low dose ($\leq$200 mg over 1 month). Formulation comparison was administration of ferric gluconate versus iron sucrose over 1 month. Outcomes were hemoglobin, epoetin dose, transferrin saturation, and serum ferritin during 6 weeks of follow-up.

RESULTS: We identified 117,050 patients for the dosing comparison, and 66,207 patients for the formulation comparison. Bolus dosing was associated with higher average adjusted hemoglobin (+0.23 g/dL; 95% confidence interval [CI], 0.21-0.26), transferrin saturation (+3.31%; 95% CI, 2.99-3.63), serum ferritin (+151 μg/L; 95% CI, 134.9-168.7), and lower average epoetin dose (−464 units; 95% CI, −583 to −343) compared with maintenance. Similar trends were observed with high-dose iron versus low-dose. Iron sucrose was associated with higher adjusted average hemoglobin (+0.16 g/dL; 95% CI, 0.12-0.19) versus ferric gluconate.

CONCLUSIONS: Strategies favoring large doses of intravenous iron or iron sucrose lead to improved measures of anemia management. These potential benefits should be weighed against risks, which currently remain incompletely characterized.

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KEYWORDS: Anemia; Hemodialysis; Intravenous iron

Intravenous (IV) iron is now an integral component of anemia management among patients with end-stage renal disease.[1] Originally considered an adjuvant to erythropoiesis-stimulating agents (ESA), its use has steadily increased over the past decade.[2] In the US, contemporary practice patterns for IV iron vary by both dose and formulation. For example, some dialysis clinics administer large repletion or bolus doses of iron over consecutive dialysis sessions on an intermittent, as-needed basis.[3] Others provide low-dose administrations of iron every 1 to 2 weeks to maintain iron stores,[4] or a combination of maintenance and bolus dosing.[3] Currently, intravenous iron preparations primarily consist of iron sucrose and ferric

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gluconate despite the availability of 5 different agents. Both formulations are iron-carbohydrate complexes, but possess varying pharmacokinetic and pharmacodynamic properties that may differentially affect anemia management.[5-7]

Despite the growing use of iron, there are sparse contemporary data about the benefits of IV iron use in the US dialysis population. Previous studies of dosing patterns have not directly compared dosing strategies that are now used in practice.[8,9] Furthermore, they have limited sample size and follow-up, potentially reducing generalizability to patients currently receiving dialysis. Studies comparing ferric gluconate and iron sucrose have similar limitations.[10,11]

To address this gap in the literature, we conducted a large-scale observational study using data from one of the largest national dialysis providers linked with the US Renal Data System (USRDS). Our goal was to examine the comparative effectiveness of dosing strategies and formulation types on clinical parameters of anemia management—hemoglobin level, epoetin alfa (EPO) dose, transferrin saturation (TSAT), and serum ferritin—in a cohort that is representative of contemporary patients receiving hemodialysis.

CLINICAL SIGNIFICANCE

- Large doses of intravenous iron lead to a higher hemoglobin level and lower erythropoietin dose than smaller doses of iron.
- Iron sucrose leads to higher hemoglobin levels than ferric gluconate.
- The benefits of large doses of intravenous iron come at an unknown cost because there are limited data about its safety.

METHODS

Data Sources

The data used for this study came from the clinical research database of a large dialysis provider and the USRDS. The dialysis provider owns and manages over 1500 outpatient dialysis facilities located throughout the US in urban, rural, and suburban areas. Their clinical database captures detailed clinical, laboratory, and treatment data on patients receiving care at all of their dialysis units. All data are collected using standardized electronic health record systems. For this study we used the clinical data to obtain detailed information on iron formulation and dosing, ESA use and dosing, and clinical laboratory values (eg, hemoglobin, transferrin saturation, serum ferritin). We also used data from the USRDS, a national data system that collects, analyzes, and distributes information about the treatment of end-stage renal disease in the US. Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the USRDS collaborates with several entities, including the Centers for Medicare and Medicaid Services (CMS), to create a detailed data system on end-stage renal disease (ESRD) patients. Our USRDS data originated from CMS and included data from the Medical Evidence Report Form, the Medicare Enrollment database, the ESRD Death Notification Form, and the standard analytic files, which contain final action claims data.[12]

We examined 5 years of data (2004-2008) from the clinical database to identify the cohort. These data were merged with data from the USRDS to obtain information on demographic characteristics, health care use (eg, hospitalizations, outpatient care), and additional clinical characteristics (eg, comorbidities).

Study Design

We utilized a retrospective cohort design in which we established a 6-month baseline period (to identify potential confounders and effect modifiers), a 1-month iron exposure period, and a 6-week follow-up period. **Figure 1** diagrams our specific implementation of the cohort design. The index date of the exposure period was anchored on a TSAT laboratory assessment, as this information is used to guide iron administration.

Cohort Identification

Figure 2 outlines the creation of our sample. We considered a mix of incident and prevalent patients. After merging the clinical and USRDS data, we identified individuals who had one or more TSAT laboratory assessments between January 30, 2004 and November 30, 2008. The January 30 date was chosen to allow for a month of dialysis, which is typically followed by a TSAT lab. The November 30 date was chosen to allow for the 1-month exposure period and at least 1 day of follow-up (December 31, 2008).

Data on TSAT labs were excluded if the patient:

- Had a dialysis vintage <9 months (which accounted for the 6-month baseline period and an additional 3 months from the start of dialysis to allow for stability in the CMS claims processing);[12]
- Was not in center hemodialysis for the baseline and exposure period;
- Did not have Medicare Part A and Part B coverage;
- Received iron dextran or both ferric gluconate and iron sucrose in the exposure period;

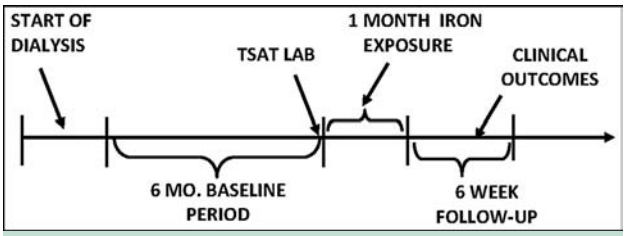

Figure 1 Study design. TSAT = transferrin saturation.