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Original Investigation

Comparative Short-term Safety of Sodium Ferric Gluconate Versus Iron Sucrose in Hemodialysis Patients

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Background: Despite different pharmacologic properties, little is known about the comparative safety of sodium ferric gluconate versus iron sucrose in hemodialysis patients.

Study Design: Retrospective cohort study using the clinical database of a large dialysis provider (2004-2005) merged with administrative data from the US Renal Data System.

Setting & Participants: 66,207 patients with Medicare coverage who received center-based hemodialysis.

Predictors: Iron formulation use assessed during repeated 1-month exposure periods (n = 278,357).

Outcomes: All-cause mortality, infection-related hospitalizations and mortality, and cardiovascular-related hospitalizations and mortality occurring during a 3-month follow-up period.

Measurements: For all outcomes, we estimated 90-day risk differences between the formulations using propensity score weighting of Kaplan-Meier functions, which controlled for a wide range of demographic, clinical, and laboratory variables. Risk differences were also estimated within various clinically important subgroups.

Results: Ferric gluconate was administered in 11.4%; iron sucrose, in 48.9%; and no iron in 39.7% of the periods. Risks for most study outcomes did not differ between ferric gluconate and iron sucrose; however, among patients with a hemodialysis catheter, use of ferric gluconate was associated with a slightly decreased risk for both infection-related death (risk difference, −0.3%; 95% CI, −0.5% to 0.0%) and infection-related hospitalization (risk difference, −1.5%; 95% CI, −2.3% to −0.6%). Bolus dosing was associated with an increase in infection-related events among both ferric gluconate and iron sucrose users.

Limitations: Residual confounding and outcome measurement error.

Conclusions: Overall, the 2 iron formulations studied exhibited similar safety profiles; however, ferric gluconate was associated with a slightly decreased risk for infection-related outcomes compared to iron sucrose among patients with a hemodialysis catheter. These associations should be explored further using other data or study designs.

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INDEX WORDS: Anemia; chronic kidney disease (CKD); end-stage renal disease (ESRD); hemodialysis (HD); intravenous iron formulations; sodium ferric gluconate; iron sucrose; mortality; infection; hospitalization; cardiovascular events; safety.

Anemia is common among patients with end-stage renal disease (ESRD)[1] and is associated with increased morbidity, mortality, and risk for hospitalization.[2] The anemia seen in these patients is primarily caused by impaired production of endogenous renal erythropoietin. It is worsened by depletion of iron reserves caused by hemodialysis-related blood loss and poor intestinal absorption of iron.[3] Erythropoiesis-stimulating agents are the primary treatment for the anemia of ESRD. The iron deficiency is addressed through administration of intravenous (IV) iron formulations and, much less effectively, oral iron supplementation.[4]

Currently, there are 6 formulations of IV iron available on the US market: low-molecular-weight iron dextran, high-molecular-weight iron dextran, iron sucrose, sodium ferric gluconate, ferumoxytol, and ferric carboxymaltose. High-molecular-weight iron dextran has been linked to hypersensitivity reactions, including anaphylaxis,[5,6] and carries a black box advisory on its

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label. Consequently, there is currently little use of iron dextran in the US dialysis population. Ferumoxytol was approved by the US Food and Drug Administration in 2009 and is not widely used; ferric carboxymaltose was approved in 2013, but remains labeled for use in non−dialysis-dependent chronic kidney disease. Thus, the iron formulations most commonly used in the US ESRD population are sodium ferric gluconate and iron sucrose.

Sodium ferric gluconate and iron sucrose preparations are iron-carbohydrate complexes or colloids of varying molecular size with a spheroid iron-carbohydrate core. Because of differences in core size, carbohydrate chemistry, and molecular weight, the 2 formulations have different pharmacokinetic and pharmacodynamic properties.[7] Despite concerns about oxidative stress and infection risk associated with the use of IV iron,[8,9] pharmacologic differences between the different iron formulations,[7] and apparent differences in effectiveness,[10] there is currently little information about the comparative safety of ferric gluconate versus iron sucrose.[11] To address this evidence gap, we conducted a large-scale comparative safety study of ferric gluconate versus iron sucrose in a cohort of patients undergoing maintenance hemodialysis.

METHODS

Data Sources

The data used for this study came from the clinical research database of a large dialysis provider and the US Renal Data System (USRDS), which were merged at the patient level. The dialysis provider owns and manages more than 1,500 outpatient dialysis facilities located throughout the United States in urban, rural, and suburban areas. Their clinical database captures detailed clinical, laboratory, and treatment data for patients receiving care at all 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 about iron formulation use and dosing, erythropoiesis-stimulating agent use and dosing, clinical laboratory values (eg, hemoglobin, transferrin saturation [TSAT], and serum ferritin), current vascular access, and recent IV antibiotic use. The USRDS is a national data system funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that collects, analyzes, and distributes information about the treatment of ESRD. USRDS includes 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] These data were used to obtain information about demographic characteristics, health care use (eg, hospitalizations and outpatient care), and additional clinical characteristics (eg, comorbid conditions).

We examined clinical data from 2 years (2004-2005) during which the dialysis provider used both ferric gluconate and iron sucrose. After 2005, the dialysis provider used mostly iron sucrose.

Study Design

We used a retrospective cohort design with repeated measures on iron treatments and outcomes. The index date of the 1-month exposure assessment period was anchored on a TSAT measurement because this information is used to guide iron administration. The 6-month baseline period prior to the TSAT measurement was used to identify potential confounders and effect modifiers. Patients were followed up for 3 months after the exposure period. Eligible patients could contribute multiple exposure/follow-up periods (Fig 1). Our design was implicitly attempting to mimic a randomized trial in which patients prescribed a 1-month course of iron were randomly assigned to receive the iron as either ferric gluconate or iron sucrose and then followed up for 90 days, with further iron treatment decisions left to the discretion of the physician.

Cohort Identification

We first identified center-based outpatient hemodialysis patients defined as follows: individuals who had undergone at least 9 months of maintenance dialysis (which accounted for the 6-month baseline period and an additional 3 months from the initiation of dialysis therapy to allow for stability in the Centers for Medicare & Medicaid Services claims processing),[12] received hemodialysis in a dialysis facility, were covered by Medicare Parts A and B, and had at least one TSAT measurement during January 30, 2004, to November 30, 2005 (the November 30 date was chosen to allow for the 1-month exposure period and at least one day of follow-up). Patients were excluded if they had polycystic kidney disease because anemia management may be considerably different in these patients. TSAT records were excluded if: (1) iron dextran or both ferric gluconate and iron sucrose were delivered in the exposure period; (2) the duration of Part A claims prior to index was insufficient (ie, <120 days of Part A claims), suggesting

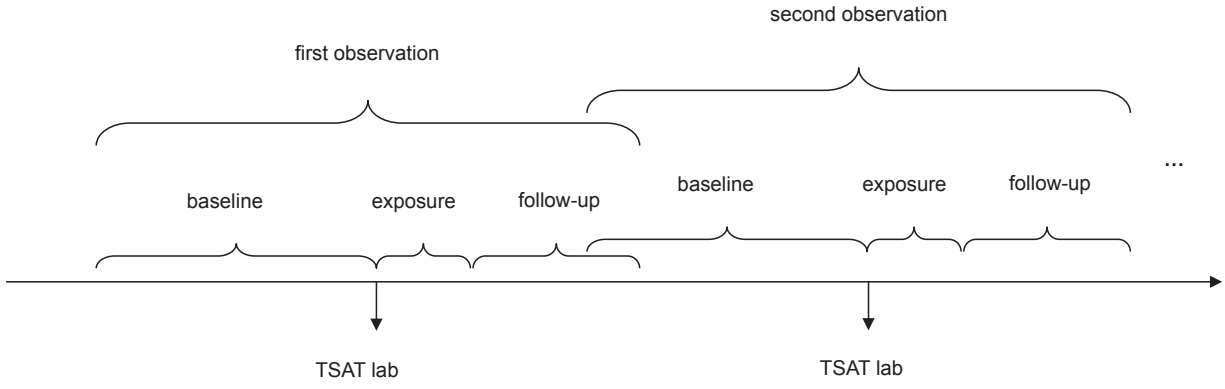

Figure 1. Study design schematic. Abbreviations: lab, laboratory; TSAT, transferrin saturation.