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Original Investigation

Safety of Intravenous Iron in Hemodialysis: Longer-term Comparisons of Iron Sucrose Versus Sodium Ferric Gluconate Complex

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Background: Controversy exists about any differences in longer-term safety across different intravenous iron formulations routinely used in hemodialysis (HD) patients. We exploited a natural experiment to compare outcomes of patients initiating HD therapy in facilities that predominantly (in ≥90% of their patients) used iron sucrose versus sodium ferric gluconate complex.

Study Design: Retrospective cohort study of incident HD patients.

Setting & Participants: Using the US Renal Data System, we hard-matched on geographic region and center characteristics HD facilities predominantly using ferric gluconate with similar ones using iron sucrose. Subsequently, incident HD patients were assigned to their facility iron formulation exposure.

Intervention: Facility-level use of iron sucrose versus ferric gluconate.

Outcomes: Patients were followed up for mortality from any, cardiovascular, or infectious causes. Medicare-insured patients were followed up for infectious and cardiovascular (stroke or myocardial infarction) hospitalizations and for composite outcomes with the corresponding cause-specific deaths.

Measurements: HRs.

Results: We matched 2,015 iron sucrose facilities with 2,015 ferric gluconate facilities, in which 51,603 patients (iron sucrose, 24,911; ferric gluconate, 26,692) subsequently initiated HD therapy. All recorded patient characteristics were balanced between groups. Over 49,989 person-years, 10,381 deaths (3,908 cardiovascular and 1,209 infectious) occurred. Adjusted all-cause (HR, 0.98; 95% CI, 0.93-1.03), cardiovascular (HR, 0.96; 95% CI, 0.89-1.03), and infectious mortality (HR, 0.98; 95% CI, 0.86-1.13) did not differ between iron sucrose and ferric gluconate facilities. Among Medicare beneficiaries, no differences between ferric gluconate and iron sucrose facilities were observed in fatal or nonfatal cardiovascular events (HR, 1.01; 95% CI, 0.93-1.09). The composite infectious end point occurred less frequently in iron sucrose versus ferric gluconate facilities (HR, 0.92; 95% CI, 0.88-0.96).

Limitations: Unobserved selection bias from nonrandom treatment assignment.

Conclusions: Patients initiating HD therapy in facilities almost exclusively using iron sucrose versus ferric gluconate had similar longer-term outcomes. However, there was a small decrease in infectious hospitalizations and deaths in patients dialyzing in facilities predominantly using iron sucrose. This difference may be due to residual confounding, random chance, or a causal effect.

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INDEX WORDS: Intravenous iron; iron sucrose; sodium ferric gluconate complex; mortality; cardiovascular; safety; infectious hospitalization; myocardial infarction; stroke; hemodialysis; end-stage renal disease (ESRD); dialysis facility formulary; natural experiment.

Patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis (HD) have been estimated to lose 1 to 2 g of iron per year (in some patients, as much as 4-5 g annually)[1] from a combination of subclinical or overt bleeding events, which are common in this population,[2] as well as through blood retained in and discarded with the extracorporeal circuit after each HD treatment.

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Because this iron loss exceeds what these patients can usually replace through intestinal absorption,[3] most HD patients depend on intravenous iron supplementation to remain iron replete and optimize their response to treatment with erythropoiesis-stimulating agents. However, intravenous administration of iron is unphysiologic and circumvents biological systems in place to control iron balance and minimize the appearance of non–transferrin-bound iron in the circulation. In addition to the extremely rare event of acute and sometimes life-threatening anaphylaxis, concerns have lingered for decades about potential longer-term consequences such as infectious and cardiovascular events that may be mediated via immunologic, inflammatory, and oxidative stress pathways.[1] Little attention has been given to any putative differences in longer-term safety among available iron formulations, which are structurally heterogeneous iron-carbohydrate nanoparticle complexes with considerably different pharmacologic stability and pharmacokinetic properties.[4] Almost no randomized or observational evidence exists on the comparative outcomes among intravenous iron formulations in ESRD, and the few studies that exist had small sample sizes and/or very limited follow-up.[5-7]

We conducted the present study to fill this evidence gap and compared longer-term safety between the 2 intravenous iron formulations predominantly used for patients with ESRD receiving HD in the United States: iron sucrose and sodium ferric gluconate complex. We used an innovative design that exploited the natural experiment that arose when dialysis facilities treated all or almost all their patients with a single iron formulation.

METHODS

Rationale

Most dialysis centers restrict the choice among injectable medications of a class, for example, among erythropoiesis-stimulating agents, intravenous iron preparations, or vitamin D analogues, and often have formularies in place that require that all or almost all patients receive the preferred agent. These center-level decisions can be considered natural experiments if centers predominantly using one drug versus another do not differ systematically in other aspects of their care and, on average, the characteristics of their patients. If these assumptions hold true, the center can serve as an instrument and patient exposure defined on the predominant practice pattern of each center. We have recently used this design in 2 comparative safety studies of erythropoiesis-stimulating agents and of ferumoxytol, and the following resembles the methods described therein.[8,9] This approach is particularly attractive for the intermittent nature of iron treatment, for which iron storage parameters and (temporary and sometimes relative) contraindications will lead to potentially strong and partly unobserved time-dependent confounding that may be difficult to accommodate using traditional or novel (marginal-structural models) methods for time-dependent exposures.

Study Population: Patient Selection, Exposure Assignment, and Follow-up

From the US Renal Data System (USRDS), the national ESRD registry, we recorded from billing codes to Medicare all intravenous iron administrations for January 1, 1999, to December 31, 2011. For each HD center and calendar month, we then defined the proportion of intravenous administrations for iron sucrose versus sodium ferric gluconate complex versus other (iron dextran and ferumoxytol). For each center, we termed a calendar month an iron sucrose center-month if ≥90% of administered intravenous iron administrations in that center and month were iron sucrose. Similarly, if ≥90% of administrations were ferric gluconate, we considered it a ferric gluconate center-month. All other center-months were categorized as "mixed/other." Because we were interested in studying "mature" use of each iron formulation of interest, centers were required to have predominantly used the same formulation for at least 12 months prior to being eligible to contribute patients to the study cohort. Centers were then described by their geographic region (Northwest, Midwest, South, and West), chain affiliation (yes vs no), and whether they were free standing or hospital based, and pairs of 1 iron sucrose and ferric gluconate center each were hard-matched on these characteristics and calendar year.

Following the matching month, we enrolled all patients regardless of their insurance status who had incident ESRD and initiated HD therapy in an iron sucrose facility and its matched ferric gluconate facility. If a facility switched back from predominant use of iron sucrose or ferric gluconate, respectively, both matched facilities were no longer eligible to contribute new patients to the study and all existing patients in the matched set were censored for further follow-up. Because iron therapy is usually intermittent, depending on iron status measurements, dosing approach (bolus vs maintenance), and potential temporary contraindications (eg, infections), included patients may have received continuous, intermittent, or no iron treatment at all during follow-up. However, if treated, they usually received the intravenous iron formulation identified as predominantly used by their facility at the time.

The closed cohort that was selected this way was then followed up for all-cause and cause-specific (cardiovascular, infectious, and other) mortality because mortality is recorded in the USRDS regardless of insurance status and payor type. Patients were censored at the end of the database (December 31, 2011), upon switching to peritoneal dialysis therapy, and when receiving a kidney transplant, switching to another HD facility, or their facility or its match switched to predominant use of another intravenous iron formulation as described in detail in previous paragraph.

We used Medicare billing claims for the study of nonfatal outcomes. To do so, we identified the subsample of patients who survived 90 days from initiation of dialysis therapy and whose primary payor at day 91 was Medicare (Parts A + B). By federal mandate, most patients with ESRD qualify for Medicare coverage at the beginning of the fourth month after incident ESRD regardless of their age. Patients were followed up from day 91 after initiation of HD therapy until censoring for the forelisted reasons, as well as at loss of Medicare Parts A plus B coverage or if they died. In this subcohort, we also plotted for each month of follow-up the percentages of patients receiving iron sucrose versus ferric gluconate to demonstrate the validity of using facility preference as the proxy for actual exposure over time. We further plotted mean hemoglobin concentrations and monthly doses of erythropoiesis-stimulating agents to investigate whether differences between study groups existed in other anemia management aspects.

Patient Characteristics

From the USRDS patient file, we ascertained patients' age, sex, race (white, black, Asian, or other), and ethnicity (Hispanic vs