Is Intravenous Iron Supplementation Safe to Administer to Patients on Hemodialysis with Active Infection—What Do We Know, and What More Do We Need to Know?

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When treating patients with CKD on hemodialysis with active infection, a key tenet is do no harm. CKD is a major public health problem that consumes a disproportionate and increasing share of health care resources. Treating CKD was estimated to cost Medicare $44.6 billion in 2014, although there is considerable under-recognition of CKD (1). Mainstays of treatment options for anemia are erythropoiesis-stimulating agents (ESAs) and intravenous iron. However, iron supplementation is a double-edged sword. Iron administration allows patients to achieve increased hemoglobin levels with lower doses of ESAs than without iron administration. Iron supplementation also places patients with CKD on dialysis at greater risks of oxidative stress, cardiovascular diseases, and possibly, infection (2). Prospective research directly linking intravenous iron to exacerbation of existing infection or infection-related mortality is lacking.

Ishida et al. (3) examined statistical associations between intravenous iron and clinical outcomes among patients with kidney disease hospitalized for infection. On the basis of analyses of US Renal Data System databases, Ishida et al. (3) conducted a retrospective observational cohort study of 23,000 adult patients on hemodialysis hospitalized for bacterial infection. All patients had received iron treatment before their hospital admission, but only 10% continued having intravenous iron during their hospital stay. Continued iron in this patient group was not associated with increased risk of all-cause 30-day mortality, mortality in 2010, length of hospital stay, and readmission for infection or death within 30 days of discharge.

The results of the study by Ishida et al. (3) are interesting and important. It is reassuring to review a large-scale observational data analysis reporting that iron administration to patients on hemodialysis with serious infections is not associated with increased rates of early mortality or readmission for infection. However, the basic issue is whether this study provides convincing evidence that iron can be safely administered in this setting. Observational studies have limitations. A major limitation is patient selection. It is not known why 10% of the patients were chosen to stay on iron and 90% were not. Eager to follow guidelines advising against iron administration in the setting of active infection among patients with CKD on dialysis, most physicians possibly avoided iron, and hence, the majority of patients were excluded from receiving it. A cynic might say that this study showed that intravenous iron is relatively safe when limited to a few carefully selected patients. Measured outcomes did not include infections but rather, included only those infections serious enough to lead to hospitalization. The only outcome on infections was readmission for infection. The association between iron use and milder infections is left to later studies.

The study was novel in its evaluation of the potential adverse consequences of withholding iron during infection (3). The great majority of patients did not receive iron during hospitalization. These patients did not have higher blood transfusion rates, although Ishida et al. (3) are cautious in drawing conclusions because of the rare nature of transfusions.

Are there other data sources that might be useful here? Clinical trials are one option, bearing in mind that traditional premarketing studies cannot reliably detect rare but potentially important adverse events. Himmelfarb and Tuttle (4) recommend new approaches to pre-approval clinical trials, so that drugs with unexpected off-target effects can be rapidly identified. These approaches, including tools such as “human organs on microchips,” while proposed for new therapies for patients with CKD, can be extended to old therapies, such as iron supplementation (4).

Ongoing National Institutes of Health–funded pharmacovigilance initiatives are another consideration. One initiative, the Southern Network of Adverse Reactions, rapidly reported unexpected occurrences and high rates of severe and occasionally fatal anaphylaxis/hypotension minutes after a novel ESA, peginesatide, was administered to patients with CKD on dialysis (5). This work was on the basis of evaluation of adverse events identified by clinicians associated with the largest dialysis organization in North America in the context of a phase IV observational study. Moving forward, the large dialysis organization has the infrastructure and capacity to design, conduct, and evaluate a phase IV randomized clinical trial evaluating
iron supplementation in the setting of active infection of patients with CKD on dialysis. Another option is the Food and Drug Administration–funded SENTINEL effort, particularly if large database analyses and electronic medical record reviews can provide information on the safety of iron administration to patients with CKD on dialysis with active infections.

In the meantime, as noted by Himmelfarb and Tuttle (4), given escalating human and societal costs of kidney disease, efforts to find safe and effective therapies are vital. We hope that iron is one such treatment, but clinical trials may be the only way to definitively answer this question.

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References


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