Intravenous Iron: How Much Is Too Much?

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Anemia is associated with poor cardiovascular and global outcome in patients with chronic kidney disease (CKD) (1). The correction of anemia requires epoetin in most instances. This in turn generally requires intravenous iron supplementation to avoid iron-deficiency and to achieve optimal results. High iron doses have been shown to decrease epoetin needs and to make anemia treatment more cost effective.

The optimal strategy to cover the iron needs of CKD patients remains a matter of debate. The main reason for this is the absence of controlled randomized trials. Commercial pressure also comes into play. Nobody would disagree with the statement that excessive iron load is harmful for CKD patients, as it is for patients without renal disease. The question then is how to avoid iatrogenic iron overload in individuals who need supplemental iron in addition to dietary sources. One could elect to favor the oral route. With oral iron supplementation, the danger is minimal in presence of an intact intestinal barrier. Not so with intravenous iron, where no such barrier exists. The problem is that in patients with stage 4 to 5 CKD, oral iron supplements often are not useful because of poor enteric absorption and limited gastrointestinal tolerance. Therefore, the intravenous route has become the preferred mode of administration in most instances, at least in hemodialysis patients.

The next question is whether there is a threshold of iron overload and, if so, whether it can be reliably defined. Before addressing this major issue, at least from a clinical point of view, let us raise a number of related questions first. To what extent is it important to distinguish acute from chronic intravenous iron overload? What is the importance of the amount of iron given per injection, as compared with the total amount given per month or year (*e.g.*, consider administering 40 mg × 3 doses/week = 480 mg/4 wk *versus* 480 mg once every 4 wk)? Should iron be infused slowly, possibly depending on the type of iron preparation used, or does the infusion rate not matter? Does the type of iron salt or iron complex used play a role? Note that different preparations could release bioactive iron more or less easily (2).

From a pathophysiologic point of view, when considering potential complications caused by intravenous iron administration, it is also important to separate iron toxicity from adverse allergic reactions induced by various iron preparations. Should major efforts be directed at avoiding acute allergic events, which, though rare, may be lethal, or should efforts mostly be directed at preventing acute or chronic iron toxicity? Is it more important to avoid acute, repeated, noxious effects *via* the generation of bioactive iron and the induction of oxidative stress, or to avoid chronic iron overload with deleterious effects *via* various mechanisms including enhanced bacterial growth and infection?

Unfortunately, we have only fragmentary and often contradictory answers to most of these questions, based on experimental studies and observational studies in humans. Evidence from experiments in isolated cell systems and animals shows that iron excess can exert cytotoxicity, enhance oxygen radical generation, inhibit neutrophil activity, promote atherosclerosis, exacerbate sepsis, and increase mortality (3–7). In hemodialysis patients, the acute administration of high iron doses enhances oxidative stress (8–10). These studies have used various timing protocols, different iron preparations, and different markers of oxidative stress. The report by Roob *et al.* (10) has also demonstrated that a single dose of vitamin E can attenuate lipid peroxidation in hemodialysis patients who receive intravenous iron during the dialysis session. We observed in chronic hemodialysis patients a direct association between the dose of iron administered and the degree of intima-media thickness, an early sign of atherosclerosis (11). It must be pointed out, however, that other authors failed to observe such noxious effects and took issue with some of the conclusions reached in the reports above.

Observational studies performed in large study cohorts do not allow definitive conclusions either. Feldman *et al.* showed in a first report a significant excess mortality in 5833 hemodialysis patients who had received >1000 mg iron intravenously over a 6-mo period (12). In contrast, in a second study performed in a different cohort of 32,566 hemodialysis patients, Feldman *et al.* (13) failed to identify a statistically significant association between any level of iron administration and mortality. The authors attributed their initial positive finding to the existence of unidentified confounders.

In this issue of *JASN*, Kalantar-Zadeh *et al.* (14) used a similar approach to address the question of a possible association between iron overload and mortality. In addition, the authors asked at the outset whether the positive associations found between parameters of iron stores and outcome in some previ-

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ous studies might be confounded by the presence of inflammation and malnutrition. They analyzed data from a cohort of 58,058 hemodialysis patients and found, after appropriate adjustments, that patients with serum ferritin between 200 and 1200 ng/ml, serum iron between 60 and 120 μg/ml, and a transferrin saturation ratio between 30 and 50% were at the lowest risk of cardiovascular and all-cause mortality, compared with patients in whom same iron parameters were outside these ranges. Of note, patients who received >400 mg intravenous iron per month tended to have increased death rates, whereas those who received lower doses were at lower mortality risk, compared with those who received no intravenous iron at all. The authors speculated that the association of serum ferritin levels >800 ng/ml with higher death rates observed in the unadjusted model was mostly due to confounding by inflammation and malnutrition. However, a direct cardiovascular toxicity of iron administration and storage has not been entirely excluded. It could actually just have been outweighed by these latter two prevalent factors. A separate analysis in patients with high ferritin levels, *i.e.*, >500 ng/ml, but no inflammation or malnutrition could answer this point.

The finding of a beneficial effect of intravenous iron doses up to 400 mg per month is not unexpected. However, this does not tell us whether it is preferable to administer 400 mg of iron or less in many small, separate doses or in one large dose per month. We also do not know whether the type of iron preparation matters, because the patients of this cohort initially received three different types of intravenous iron compounds, namely iron gluconate, sucrose, and dextran, whose relative administration varied markedly over the 2-yr time period. Thus, during the first quarters iron gluconate was administered to >90% of iron-receiving patients, whereas in the last quarters the proportion was only 5 to 10% and iron sucrose became the dominant form.

This observational study had a number of other possible limitations, most of which have been acknowledged by the authors. The study population examined was a mixed incident/prevalent maintenance hemodialysis population, bearing the possibility of selection bias. The number of cases included with gastrointestinal bleeding, other sources of blood loss, or malignancies was not known. Such causes may lead to low serum iron levels and poor outcome, representing possible confounders that have not been taken into account. Similarly, patients with intercurrent infection or systemic inflammatory diseases were not excluded; again, this may have favored low serum iron parameters. The type of vascular access, native arteriovenous fistula *versus* arteriovenous graft, might have constituted an additional confounding variable. Finally, the doses of iron which have been actually administered might have been lower than the billed doses, and possible differences might differ according to the type of intravenous medication administered.

In the end, we agree with Kalantar-Zadeh *et al.* (14) that the associations found in their study, similar to the ones reported in previous studies, should not be interpreted as causal relationships between intravenously administered iron and improved survival. They merely provide indications of possible relationships, which need to be investigated in prospective, randomized and controlled trials. The latter should address the questions raised above about optimal iron amount and formulation and optimal intravenous administration mode. In addition, they also should define adequate ranges of iron store parameters for hemoglobin values within the optimal range for dialysis patients. An intermediate end point such as vascular reactivity, *e.g.*, flow-mediated dilation, could be used to evaluate the safety of iron administration and storage in such patients (15). In the meantime we prefer, like Aronoff (16), to follow the old Roman proverb "*Primum nil nocere*"(do not harm) and stick to present guidelines, which recommend that intravenous iron be withheld for transferring saturation (TSAT) > 50% and/or serum ferritin > 800 ng/ml according to Kidney Disease Outcomes Quality Initiative (KDOQI) (17), or for serum ferritin > 500 ng/ml and/or TSAT > 40% according to European Best Practice Guidelines (18).

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See related article, "Time-dependent Associations between Indices of Iron Store and Mortality in Hemodialysis Patients," on pages 3070–3080.