Iron toxicity: relevance for dialysis patients

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ABSTRACT

Iron deficiency is common among patients with advanced kidney disease, particularly those requiring hemodialysis. Intravenous iron is a convenient treatment to supplement iron and is widely used among hemodialysis patients. Its efficacy is well established that, with treatment, hemoglobin levels rise and erythropoiesis-stimulating agent dose requirements are reduced. However, the safety of intravenous iron with respect to patient-centered outcomes has not been adequately studied. A variety of studies have indicated potential safety concerns, but most have been of small numbers of patients and with end points studied that have unclear clinical relevance. In this study, issues related to iron toxicity are reviewed.

Keywords: anemia, iron, toxicity

IRON DEFICIENCY IN THE HEMODIALYSIS PATIENT

Iron deficiency is a common contributing cause of anemia in the hemodialysis patient. Frequent blood drawing for laboratory tests, surgical procedures for vascular access and blood loss into the hemodialyzer and tubing all contribute to iron loss. The average hemodialysis patient loses 1–2 g of iron per year through these mechanisms [1]. In addition, iron absorption from diet is diminished due to inflammation and medications, such as gastric acid inhibitors and phosphate binders. Virtually all hemodialysis patients will develop iron deficiency if iron is not replaced. In addition to absolute iron deficiency, it is recognized that dialysis patients may also have functional iron deficiency. Iron stores appear to replete by conventional criteria, but are unable to mobilize when erythropoiesis is stimulated by an erythropoiesis stimulating agent (ESA) [2].

Transferrin saturation (TSAT) and ferritin levels are widely used to assess iron status and diagnose iron deficiency. These test results vary considerably even in the absence of iron depletion [3] and have limited sensitivity and specificity in the hemodialysis population [4]. Recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recognize these limitations, but recommend goal-directed intravenous (IV) iron treatment when TSAT ≤30% and serum ferritin ≤500 ng/mL [5]. A more detailed evaluation in these patients can lead to treatable alternate diagnoses such as gastrointestinal or other sources of blood loss.

TREATMENT OF IRON DEFICIENCY ANEMIA

Iron replacement in the hemodialysis patient ensures adequate iron stores for erythropoiesis. Although iron can be administered via oral or parenteral routes, intravenous dosing is preferred in hemodialysis patients. In the majority of clinical studies assessing the route of iron replacement, intravenous iron yielded a greater increase in hemoglobin (Hgb) than in oral iron [6–9]. Hemodialysis patients also have readily available vascular access, facilitating the ease of intravenous administration. For patients with anemia, a trial of goal-directed intravenous iron is suggested with TSAT ≤30% and serum ferritin ≤500 ng/mL [5]. These patients are likely to respond to iron administration, with a subsequent increase in hemoglobin. For example, a randomized controlled trial assessed the hemoglobin response to intravenous iron in hemodialysis patients. Forty-four patients were randomized either to receive a 1000 mg of intravenous sodium ferric gluconate complex or to a control group-receiving oral iron. All patients were on an ESA, but the dose was not altered during study enrollment. After 30 days, the treatment group had a greater increase in the hemoglobin level of 1.3 g/dL, compared with 0.4 g/dL in the control group (P = 0.001) [10]. One randomized controlled trial included 134 anemic hemodialysis patients with TSAT <25% and serum ferritin 500–1200 ng/mL, and randomized-treated patients to a 1000 mg dose of intravenous iron. All patients in the study received a 25% increase in an ESA dose. At 6 weeks, the treatment group had a significant increase in hemoglobin when compared with the control group [11]. Several studies have demonstrated that administration of iron
in hemodialysis patients leads to reduction in the required dose of ESA [6, 8, 9]. This has cost-saving benefits, as well as the potential to lessen the risk of ESA adverse events. For example, a randomized controlled trial of 37 hemodialysis patients assessed hemoglobin response and ESA dose requirements. Patients in the treatment group received 250 mg of intravenous iron dextran every 2 weeks. When compared with the group receiving no iron therapy, the treatment group had a greater hemoglobin response, required lower doses of recombinant human erythropoietin, and had greater cost-savings per patient [9]. Another randomized controlled trial of 52 hemodialysis patients found a 46% reduction in the mean ESA dose requirement, when comparing treatment group patients on chronic intravenous iron with control group patients on oral iron treatment [6]. Taken together, it is clear that IV iron treatment can improve Hgb and ESA dose response. These are helpful findings, but it should be noted that studies have not indicated any patient-centered benefit.

**IRON TOXICITY**

Iron is a vitally important substance for the maintenance of health and normal biological functions. For example, both erythrocyte oxygen carriage and almost all cellular adenosine triphosphate (ATP) production are dependent on iron. Yet, iron is something of a double-edged sword, it is critical for health yet highly toxic owing to its oxidative properties. As a result, the human body has highly conserved mechanisms for meticulous control of iron [12]. The hepcidin system carefully regulates iron absorption from the diet and the availability of iron from storage tissues [12]. Injection of iron directly into the circulation bypasses these protective controls, and this raises concerns regarding the safety of intravenous iron. For example, under normal conditions, humans eat ~15 mg of iron per day of which 1 mg per day is absorbed through the intestines, where hepcidin-regulated processes adjust the amount absorbed. With intravenous iron, 100 mg are injected directly into the bloodstream, bypassing intestinal control. Safety concerns are heightened by the pervasive use of IV iron in hemodialysis patients, the further increase in use in the past 2 years and the lack of any well-powered study of sufficient duration to inform on the safety of treatment.

**IRON OVERLOAD**

There are studies that have raised concern for tissue iron accumulation among hemodialysis patients. Rostoker et al. recently studied 119 hemodialysis patients. Iron in tissue was analyzed by $T_1$ and $T_2^*$ contrast magnetic resonance imaging (MRI) without gadolinium. Mild-to-severe hepatic iron overload was present in 84% of patients, severe in 36%. There was a strong correlation between IV iron dosing and hepatic iron storage [13]. These are concerning findings but limited by inability to determine whether iron was present normally in reticuloendothelial tissues or pathologically in hepatic parenchymal cells. Similar results were obtained previously by Canavese et al., with superconducting quantum interference noninvasive magnetic measurements of nonheme hepatic iron content [14]. These results were similar to those of Rostoker; the prevalence of iron overload was high. In the pre-ESA era, Ali et al. performed autopsies and found severe hepatosplenic siderosis in 36% of patients. In addition, iron deposits were abundant in the adrenal glands, lymph nodes and lungs and were sparse in the heart, kidneys and pancreas [15]. Taken together, these studies indicate that tissue iron overload is probable in hemodialysis patients; however, the clinical implications are not clear. It is unlikely that IV iron results in organ damage due to excessive iron accumulation. This assertion is based on the relatively long number of years and high iron exposure required to cause injury in genetic hemochromatosis, and the lesser overall exposure in hemodialysis patients. However, excessive iron in tissues can have other toxic effects that may be more difficult to detect.

**FREE IRON AND OXIDATIVE STRESS**

The key roles of regulatory proteins, hepcidin, transferrin, ferroportin and ferritin regulate iron in the body and prevent free unbound iron from circulating in the blood stream [12]. One consequence of intravenous injection of iron and circumvention of these controls is that free unbound iron is often detectable. Kooistra et al. studied iron sucrose 100 mg in hemodialysis patients. TSAT increased to over 400%, indicating oversaturation, with abundant catalytically active iron present in the circulation. By high-performance liquid chromatography, they found a significant increase in nontransferrin-bound iron [16]. Rooyakers et al. [17] administered 100 mg iron sucrose intravenously to normal volunteers and found a 4-fold increase in nontransferrin-bound iron in plasma, a 53–70% increase in superoxide generation and a significant reduction in flow-mediated vasodilatation for several hours.

The human body has carefully conserved mechanisms to sequester iron safely so as to prevent oxidative injury, utilizing proteins such as ferritin and transferrin. Because intravenous iron may overwhelm the ability of these proteins to ligand iron, iron may become free in circulation or present in excess in tissues, where iron’s oxidative properties can be injurious. Poorly ligated iron can react with hydrogen peroxide (Fenton reaction) resulting in the generation of hydroxyl radicals. Iron is converted back to its Fe$^{2+}$ form by the Haber–Weiss reaction. In this process, continued substrate for ongoing iron-catalyzed hydroxyl radical production and oxidative stress is perpetuated. Hydroxyl radicals are highly toxic, resulting in denaturing of lipids, proteins and DNA [18]. This is not an unusual phenomenon, as described by Kell [19], free iron-induced reactive oxygen species (ROS) are a common cause of damage in a large number of diseases.

Intravenous iron preparations have been clearly demonstrated to induce oxidative stress and cytotoxicity in vitro, in animals, in normal human volunteers and in dialysis patients. In tissue culture, IV iron causes oxidative stress and cellular damage in endothelia cells [20]. A single injection of iron dextran (500 mg/kg) to 5/6 nephrectomized rats has resulted in oxidative stress in cardiovascular tissues for several weeks.
Dialysis patients experience a rapid rise in plasma lipid peroxidation, and DNA and protein oxidation following IV iron administration [23, 24]. In a recent crossover study, Pai et al. administered 100 mg of iron sucrose and 100 mg of iron dextran to 10 hemodialysis patients and 4 healthy volunteers (Figure 1). Patients were studied after the injection of one drug, then after a 2-week washout, and were also studied again after administration of the second agent. Research was conducted in the General Clinical Research Center at the University of New Mexico. Free iron was found in the circulation (nontransferrin-bound iron) after injection of both drugs, although significantly more so for iron sucrose. Among the healthy controls, there was virtually no increase in oxidative stress. In contrast, 50–83% of hemodialysis patients had increased ROS 60 and 240 min after injection. The authors suggest that because of the importance of ROS in pivotal signaling pathways, further investigation is required [25]. While most studies of intravenous iron in hemodialysis patients demonstrate induction of oxidative stress, one twist was in a study by Roob et al. These investigators studied 100 mg of iron sucrose in 22 hemodialysis patients, and like other studies found significant increases in oxidative stress. In contrast to previous studies, these authors attempted to blunt this effect with an antioxidant. Pretreatment, 6 h prior to hemodialysis with 1200 IU of all-rac-alpha-tocopheryl acetate greatly attenuated lipid peroxidation [26].

Finally, although of less relevance to dialysis patients, there have been reports of renal toxic effects of IV iron that could be related to free iron or oxidative injury. Agarwal et al. [27] studied 62 patients with chronic kidney disease (CKD), randomizing patients to treatment with IV iron sucrose or ferric gluconate. The authors found proteinuria to increase after dosing, with a greater effect of iron sucrose. Whether these transient findings have any sustained impact on renal injury remains unclear.

Taken together, the literature strongly supports at least a transient increase in oxidative stress after intravenous iron injection in hemodialysis patients. While the clinical impact cannot yet be determined, the risk and uncertainty should shift the risk benefit decision matrix toward therapeutic caution.

**IRON AND CARDIOVASCULAR DISEASE**

Cardiovascular disease is the leading cause of death in hemodialysis patients, so any negative effect of intravenous iron is highly relevant. Theoretically, oxidative stress induced by IV iron could damage vascular endothelium and accelerate atherosclerosis. Evidence is present from several sources examining this subject. In endothelial tissue culture, iron products, at relevant pharmacologic concentrations, stimulate cellular apoptosis, inhibit proliferation and cause monocyte adhesion. In an isolated arterial ring model, iron inhibited vascular relaxation [28]. Similarly, in humans, after injection of 100 mg of iron sucrose to normal volunteers, there was inhibition of vascular relaxation [17]. In apolipoprotein E-deficient mice, atherosclerotic lesions contain significant amounts of iron. A low iron diet reduces the iron content and the size of the plaques and increases plaque stability. In humans, there is a strong positive correlation between iron content and protein oxidation products in atherosclerotic plaques [29]. Serum ferritin in humans directly correlates with the amount of iron and lipid peroxides in carotid endarterectomy specimens from patients with atherosclerosis [30]. Iron may play an important role in arterial remodeling and arteriosclerosis as evidenced by experiments finding the inhibition of intimal thickening and vascular smooth muscle cell proliferation by iron chelation in rabbits [31]. Moreover, iron and lipoproteins interact to induce vascular foam cell apoptosis and plaque instability, a phenomenon related to acute cardiovascular events [12]. Drüke et al. [32] studied the effects of IV iron-induced oxidation on the vasculature. They found that a clinical measure of atherosclerosis, increased carotid artery media-intima thickness, was directly proportional to the annual dose of IV iron. Recently, van der Weerd et al. studied hepcidin-25 as a predictor of cardiovascular mortality in 405 hemodialysis patients. Hepcidin-25 is a key regulator of iron status, increased by iron overload as well as by inflammation. The investigators found hepcidin-25 to be significantly associated with fatal and nonfatal cardiovascular (CV) events [hazard ratio 1.24 per 10 nmol/L, 95% confidence interval (CI) 1.05–1.46, P = 0.01]. This was true even after adjustment for inflammation, suggesting a possible role for iron overload [33]. Taken together, these observations indicate a potential role of IV iron and iron overload in endothelial dysfunction and atherosclerosis.

Despite the potential risks of iron in relation to cardiovascular disease, it is interesting that IV iron treatment has been found to have benefit among patients with congestive heart failure (95% CI 0.13–9.80), but no relationship was found on mortality (odds ratio 0.66, 95% CI 0.30–1.44). Some of these studies have evaluated important patient-centered outcomes. A recent meta-analysis was conducted by Kapoor et al. [34]. Five randomized controlled trials involving 631 patients were analyzed. Patients treated with intravenous iron in these trials were found to have reductions in hospitalizations, improvement in

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**FIGURE 1**: Increase compared with the baseline of ROS in hemodialysis patients 60 and 240 min after injection. From Pai et al. [25], with permission from Springer.
New York Heart Association class and left ventricular ejection fraction, but no significant improvement in mortality [34].

**IRON AND INFECTION**

Another important cause of morbidity and mortality in hemodialysis patients is infection. Iron is a key cofactor for microbial growth, and the human body avidly sequesters iron when infection is present. Direct injection of iron into the circulation may bypass these controls, making iron available to microorganisms. In addition, intravenous iron may impair immune function and increase susceptibility to infection. Early studies drew attention to this subject by demonstrating a direct relationship between serum ferritin concentrations in hemodialysis patients and risk for infection [35]. Subsequent studies have had ambiguous results leaving the relationship somewhat unclear [36].

Iron overload leads to CD4+ T-cell depletion in transfusion-dependent patients. Lymphocytes are poorly equipped to sequester iron, so nontransferrin-bound iron can be toxic to these cells. This may, in part, account for immune dysfunction in patients with iron overload [35, 36]. Poorly ligated iron in circulation results in iron uptake by lymphocytes and inhibits their proliferation [37]. An example of immune dysfunction in end-stage renal disease (ESRD) patients treated with IV iron is diminished antibody production in response to hepatitis B vaccination [38]. Gupta et al. [39] found that exposure of mononuclear cells to IV iron agents induced significant intracellular oxidative stress and shortened survival in CD4+ T lymphocytes. High doses of IV iron agents impaired phagocytic activity and microbial killing capability of polymorphonuclear leukocytes [40, 41]. In a recent in vitro study [42], iron sucrose led to impaired phagocytic function and increased apoptosis of polymorphonuclear leukocytes.

Iron overload can increase the risk of infection in patients with and without CKD. There is facilitation of bacterial growth and impairment of host defense against microbial pathogens. Parkkinen et al. studied hemodialysis patients treated with IV iron sucrose, and found most of the patients to have free iron present in circulation. Blood from these patients strongly supported the growth of *Staphylococcus epidermidis* in vitro, in proportion to the amount of free iron in circulation [43]. While the clinical impact of IV iron on infection risk remains controversial, it would be prudent to avoid iron treatment until acute infections resolve.

**IRON TESTS AND SAFETY**

Serum ferritin and TSAT are the tests most commonly used to assess iron status in hemodialysis patients. It would be helpful to have upper threshold values for these tests that would define boundaries for toxicity. Unfortunately, studies repeatedly fail to find correlation between these tests and evidence of iron overload [13–15]. More importantly, the lack of studies assessing IV iron safety prevents any clear understanding of how these tests may relate to safety during therapy. The KDIGO practice guidelines suggest directed IV iron use be limited to patients with TSAT <30% and ferritin <500 ng/mL (500 μg/L) [5].

**CURRENT IRON TREATMENT PATTERNS**

There is a general perception that, at least in the USA, IV iron use is increasing in hemodialysis patients. The Dopps Practice Monitor recently found IV iron use to be increasing in the USA. For patients receiving treatment, the average dose had increased in 1 year by 39 mg per month. It would appear that this increase might be related to economic factors related to bundled dialysis reimbursement in the USA [44].

**CONCLUSION**

In conclusion, the totality of evidence raises questions as to the safety of intravenous iron treatment. All treatment decisions require a balancing of risks and benefits, informed by a strong body of evidence. For intravenous iron treatment, patient-centered benefits and risks are poorly understood. Because there is potential for toxicity of treatment, and because intravenous iron treatment is widespread, there is a need for a well-powered study of sufficient duration to better define the role of intravenous iron treatment.

**CONFLICT OF INTEREST STATEMENT**

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