Intravenous Iron Therapy in Peritoneal Dialysis Patients: Short-Term Efficacy and Long-Term Issues

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A nemia management in patients with renal disease remains a critical clinical issue. In particular, the best methods to assess iron (Fe) needs and optimal Fe replacement strategies have received ongoing attention. In this issue of CJASN, Singh et al. (1) make an important contribution by demonstrating that intravenous Fe replacement therapy (with Fe sucrose), when combined with erythropoietin (EPO), is efficacious in supporting hemoglobin (Hb) levels in chronic peritoneal dialysis (PD) patients. PD patients were entered into a multicenter, prospective, randomized trial and assigned to one of two groups. Group A received intravenous Fe sucrose + EPO, whereas group B received EPO without Fe (either intravenously or oral) supplementation. A total of 126 patients at 27 sites were randomly assigned: 80 and 46 patients into group A and group B, respectively (a 2:1 group ratio was the study objective). The Fe sucrose treatment goal was to administer 1 g of intravenous Fe, given in three divided doses over 1 mo. The primary end point was an improvement in Hb concentration. This and secondary end points (decreased need for transfusion or EPO increases; improvements in Fe stores) were monitored for 70 d after initiation of treatment.

The study met its primary objective as evidenced by a greater rise in Hb concentrations in group A versus group B patients (1.3 ± 1.1 versus 0.7 ± 1.1 g/dl; P < 0.003; means ± 1 SD). In addition, secondary end points indicated the efficacy of intravenous Fe therapy. These included less need for acute anemia intervention (1.6 versus 16.7% for groups A and B, respectively; P < 0.015) and greater improvements in Fe stores. For example, serum ferritin levels significantly increased only in Fe-supplemented patients. Fe therapy also was judged to be safe and well tolerated. For example, 78% of group A patients completed the study, versus just 56% for group B. Minimal or no serious adverse reactions to intravenous Fe were believed to occur. Furthermore, the incidence of infection was not increased with Fe therapy (a theoretical concern given that Fe is an obligate growth factor for selected fungi and bacteria). Specifically, the incidences of peritonitis and catheter-site infections were, if anything, slightly (albeit not statistically) lower in the intravenous Fe treatment group. On the basis of these results, the authors conclude that intravenous Fe, when combined with EPO, is both a safe and an effective means for combating anemia in PD patients. Therefore, this study makes an important contribution to and is supportive of the existing literature.

As with any study, questions emerge from the data, some of which may be worthy of future consideration. First, it is notable that group A patients had statistically higher baseline transferrin saturations than did the non-Fe treatment group (P < 0.005). In addition, group A patients seemed to be receiving higher EPO doses before the onset of intravenous Fe therapy (11,681 versus 7932 IU/wk for groups A and B, respectively), a difference that was close to statistical significance (P = 0.1). One wonders whether less Fe deficiency/more EPO therapy in group A patients at baseline may have had a direct impact on subsequent end points or indicated other unexplained differences between the patient groups. Second, the study was designed to select patients with relatively modest anemia (lower limit Hb “cutoff” of 9.5 g/dl; except for patients from Mexico, where entry was permitted with Hb value of 8.5 g/dl). One wonders whether even greater benefits might have accrued had more severely anemic/Fe-deficient patients been studied. Alternatively, it remains possible that more severely anemic patients would have been less responsive to Fe therapy if the worse anemia were a reflection of more severe/frequent chronic underlying illnesses. Third, it is notable that many exclusion criteria were applied. For example, “chronic” or “serious” infections, malignancy, recent major surgery, severe concomitant liver or cardiovascular disease, or asthma were some of the exclusion criteria that were used. Given that many patients with ESRD face these types of complications, it seems important to learn in the future whether any of these diseases would have a negative impact on responses to intravenous Fe therapy. Fourth, although the data certainly seem to support the safety of intravenous Fe sucrose, it is notable that patients with a history of adverse Fe sucrose reactions were excluded appropriately from the study. However, by so doing, it may be that the overall safety of Fe sucrose therapy could have been overestimated. Fifth, although Fe sucrose did improve Hb levels, the absolute increases were relatively small (A 0.6 g/dl after 70 d of treatment). Given that the group B patients had statistically lower transferrin saturations at baseline and received no Fe therapy, the improvement with intravenous Fe therapy in

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group A could be deemed to be relatively small. Certainly, these remain theoretical issues, and they do not negate the clear conclusion of the study: Intravenous Fe sucrose can be effective in raising/supporting Hb concentrations in PD patients.

It should be noted that the present study used a 1-mo Fe treatment protocol, and the follow-up period was relatively short (70 d). Therefore, it is unclear whether chronic toxicity, particularly from repetitive Fe treatment, might emerge. There have been ongoing but unsubstantiated concerns of potential adverse effects of repetitive Fe treatment in patients with pre-ESRD and ESRD. These can be divided into five areas.

1. Impact on systemic inflammation. There is no question that intravenous Fe can evoke proinflammatory effects, probably mediated via oxidative stress with secondary NF-κB activation. Indeed, experiments that were performed in rodents (e.g., [2,3]) clearly demonstrated that intravenous Fe can sensitize to the adverse consequences of endotoxemia and potentially other forms of stress. The major concern is not that Fe therapy will make Gram-negative sepsis worse in selected patients but rather whether Fe’s proinflammatory properties might worsen the chronic inflammatory state that exists in many patients with ESRD (4–6). In this regard, it would have been interesting to know whether C-reactive protein, erythrocyte sedimentation rates, or other inflammatory markers might have been altered in group A patients of the current study.

2. Impact on long-term PD efficacy. If, in fact, intravenous Fe poses a risk for inducing a proinflammatory state, then one wonders whether this might affect the peritoneum and, over the long term, alter peritoneal clearance rates. Of note in this regard are recent observations that suprapharmacologic doses of intravenous Fe, administered to mice (7), can increase peritoneal levels of monocyte chemotactic protein-1. This potent chemokine conceivably could recruit inflammatory cells to the peritoneum, induce inflammation, and secondarily have an impact on clearance. Studies to address this theoretical concern could be considered as a future area for study.

3. Effects on residual renal clearance. Residual renal function can make a significant overall contribution to total clearance in patients with ESRD. There has been a long-standing recognition that Fe is an active and potent participant in the pathogenesis of diverse forms of acute and chronic experimental nephropathies. Indeed, recent data suggest that intravenous Fe may transiently increase proteinuria in patients with renal disease (8), and glomerular Fe deposition has been noted in rodents after intravenous Fe injections (9). Furthermore, Fe-mediated increases in proximal tubular enzymbria have been noted in patients (8), and lethal experimental tubular injury may result both from oxidative stress and from mitochondrial respiratory blockade (9,10). Therefore, although the benefits of intravenous Fe, as illustrated in the present study, are clear, it seems important to make certain that Fe therapy does not change rates of renal disease progression in patients with pre-ESRD or accelerate loss of residual renal function in dialysis patients.

4. Impact of Fe on atherogenesis. Another theoretical concern is whether intravenous Fe therapy, with its known marked pro-oxidant effects, might have an adverse impact on endothelial or vascular function, culminating in an exacerbation or a progression of atherogenesis (11–18). Although there seems to be little doubt that oxidative stress is a risk factor for atherosclerosis, there as yet are no compelling data that intravenous Fe does, indeed, exert a chronic vasculopathic impact. Nevertheless, given that atherosclerosis is a major determinant of both morbidity and mortality in patients with ESRD, this would seem to be a critical issue to resolve in future studies.

5. Impact on heme oxygenase-1 (HO-1) expression. It is widely known that Fe can markedly upregulate HO-1. This stress protein generally is viewed as a potent cytoprotectant with vasodilatory as well as anti-inflammatory properties (19,20). Conversely, HO-1 can induce cytotoxicity (19,20). An interesting area for future investigation would be to ascertain the impact of intravenous Fe therapy on the expression of this critical enzyme in target organ systems and to define further any resultant downstream cytoprotective versus potential cytotoxic effects. As noted by Nath et al. (20), HO-1 can be either a protective protein or a “Trojan horse.” Therefore, the impact of intravenous Fe on HO-1 expression and the potential downstream consequences thereof remain intriguing issues for exploration.

In summary, the study by Singh et al. (1) makes an important contribution to the clinical literature by demonstrating that intravenous Fe sucrose can be efficacious in supporting Hb concentrations in PD patients. However, given that currently used Fe compounds all are highly pro-oxidant, it seems worthwhile to consider the potential long-term consequences of its administration. As illustrated by HO-1, one agent can induce both beneficial and detrimental effects. We need to consider both possibilities as chronic intravenous Fe use continues to expand.

References

5. Iseki K, Tozawa M, Yoshi S, Fukiyama K: Serum C-reactive

See related article, “Effect of Intravenous Iron Sucrose in Peritoneal Dialysis Patients Who Receive Erythropoiesis-Stimulating Agents for Anemia: A Randomized, Controlled Trial,” on pages 475–482.