

Role of Intravenous Iron Therapy in Anemia Management: State of the Art

Iron-deficiency anemia may have been first described in about 1500 BC in the Egyptian Ebers Papyrus, and treatment of the anemia with iron salts was instituted already by the mid 17th century in France. Despite its long history, iron-deficiency anemia continues to occupy center stage (30 publications in the first month of 2006), especially in developing countries, and new iron formulations continue to evolve in order to improve their tolerance and efficacy.

Anemia can result from absolute iron deficiency but also from “functional iron deficiency” as is the case in chronic diseases. Both are characterized by reduced serum iron and transferrin saturation, but ferritin is usually high in the anemia of chronic disease. In the latter, iron is sequestered in the reticuloendothelial system and is not available for erythropoiesis, resulting in “iron-restricted erythropoiesis.”

In absolute iron deficiency, iron absorption is increased and, provided there is no pathology of the gastrointestinal tract, oral iron administration usually leads to correction of the anemia, whereas in anemia of chronic disease absorption is downregulated, possibly through increased hepcidin production,¹ and the small amount of iron absorbed is directed into the reticuloendothelial system.² Parenteral iron would be a more effective mode of administration in this case, but with older formulations of intravenous iron serious adverse events were not rare. More recent formulations, however, such as iron sucrose, are better tolerated and intravenous iron administration has gained ground in Europe.³ That does not mean there are no concerns; if parenteral iron is given to patients with transferrin saturation greater than 20%, it may increase the risk of bacteremia and, in the setting of immune activation, may cause tissue damage. In anemia of chronic disease, evidence of the beneficial effect of intravenous iron in correcting the anemia is accumulating; in addition, iron, by inhibiting tumor necrosis factor- α (TNF- α), reduces disease activity.

In order to further clarify the indications for iron therapy in a number of settings, with the ultimate goal of

developing practice guidelines, the Network for Advancement of Transfusion Alternatives (NATA; www.nataonline.com) convened a panel of experts in November 2005. Areas explored were:

- Chronic renal disease
- Oncology
- Inflammatory bowel diseases
- Critical care
- Pregnancy and obstetrics
- Surgery (orthopedic/trauma, cardiac, malignancy)

Information on the relationship between erythropoietin (EPO), iron, and erythropoiesis obtained from experience with autologous blood donation was reviewed by Professor Lawrence Tim Goodnough.⁴ Under standard conditions of phlebotomy (one unit per week), without exogenous EPO administration there is a net red blood cell (RBC) volume expansion of 19%. With aggressive phlebotomy plus EPO and oral iron, RBC expansion was 40% to 50%; even patients with rheumatoid arthritis, a chronic inflammatory disease, had a similar RBC expansion. Professor Goodnough concluded that when erythropoiesis is vigorous, functional iron deficiency does occur and novel approaches to iron supplementation in these circumstances are needed.

The experience of renal anemia patients treated with EPO and iron is already substantial and, as a result, transfusion-dependent patients are few.^{5,6} Regarding intravenous iron administration, despite lingering concerns for predisposing patients to infection and oxidative stress, Professor Iain Macdougall concluded that intravenous iron both improves the anemia of renal failure even in the absence of EPO therapy and enhances patients' response to EPO administration, and that benefits outweigh these potential concerns.⁷

In oncology, the advantage of intravenous versus oral iron administration was shown in a randomized trial comparing EPO plus oral iron versus EPO plus intravenous iron in patients with chemotherapy-related anemia.⁸ Professor Heinz

Ludwig suggested, as target values for iron substitution in oncology patients, the following levels:

- Ferritin levels in the 300–500 $\mu\text{g/L}$ range
- Transferrin saturation >20%, close to 30%–40%
- Withhold parenteral iron when ferritin >1,000 $\mu\text{g/L}$, or transferrin saturation >50%

In inflammatory bowel disease, Dr Christoph Gashe presented data from a multicenter trial comparing oral and intravenous iron.⁹ In both groups, results regarding anemia correction were significant, but ferritin levels at the end of the study were significantly higher only in the intravenous group. Furthermore, in colitis patients oral iron induces oxidative stress and increases inflammation, complications that are avoided with parenteral iron.

Anemia in patients admitted to the intensive care unit was discussed by Professor Jean-Louis Vincent. An ongoing observational study of patients in hospital for less than 2 days shows an early reduction in blood iron levels, a substantial increase in ferritin levels, and a reduction in transferrin levels. Professor Vincent suggested that studies of iron metabolism are needed to identify those patients that would benefit from intravenous iron supplementation, with or without EPO administration.¹⁰

Dr Christian Breyman, discussing the anemia of pregnancy, stressed the need for aggressive intravenous iron therapy. He pointed out that the World Health Organization's efforts with regard to oral iron supplementation have failed in that the number of cases of anemia has not decreased between 1996 and 2003. In women who did not respond to oral iron, administration of intravenous iron sucrose led to a 2-g/dL increase in hemoglobin in 25 days. Experience over 14 years at the University hospital in Zurich, treating 2,000 patients using 2,500 ampoules per year, demonstrates the safety of iron sucrose in obstetrics (0.012% adverse events) as well as its efficacy. Both the number of patients and the number of blood units transfused were significantly reduced, as was the rate of postoperative infections.^{11,12}

Perioperative anemia is quite frequent, with 30% to 50% of patients anemic preoperatively and 90% postoperatively. Dr. José Garcia-Erce and Professor Manuel Muñoz commented on their experience with intravenous iron in surgery. In surgery for oncology patients, particularly those with colon cancer, preoperative administration of EPO with intravenous iron reduces the number of transfused patients. In hip replacement surgery, preliminary results of the administration of 300 mg of iron sucrose showed a reduction in the amount of blood transfused and the rate of infection, and a trend toward reduction of length of hospital stay.^{13,14} All participants agreed that, although the use of intravenous iron is increasing, further research in all areas discussed is necessary.

Although this supplement does not pretend to express a statement of a group of experts, concerning intravenous iron use in clinical practice, it does, however, give a complete picture of the state of the art of intravenous iron therapy in different settings of anemia. We hope that this special issue of

Seminars in Hematology will greatly help clinicians in their daily confrontation with anemia.

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