ADVANCES IN HEMATOLOGY

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New Paradigms and Therapies for Iron Replacement in Iron Deficiency Anemia

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H&O Who is a candidate for iron replacement?

MA Anyone who is iron deficient is a candidate for iron replacement. Examples include women who are pregnant or have heavy uterine bleeding, people with inflammatory bowel disease (IBD) or a hereditary bleeding disorder such as hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu syndrome), those who have undergone gastric bypass or multiple surgical procedures, those with stomach or colorectal cancer, and anyone with malabsorption. Approximately 3 billion people around the world have iron deficiency, and countless causes exist.

Based on high-quality neonatal literature, screening pregnant women for iron deficiency—not just anemia—appears prudent. I am conducting a trial right now in which we are seeing that nearly 40% of gravidas presenting in the first trimester without anemia are iron-deficient based on the percent saturation of transferrin.

H&O How should iron deficiency be managed?

MA The standard treatment for mild, uncomplicated iron deficiency without active bleeding is oral iron. Anyone who is unresponsive to or intolerant of oral iron should be treated with intravenous (IV) iron.

Approximately 70% of people who receive oral iron report significant gastrointestinal (GI) perturbation, which markedly decreases adherence. One strategy for reducing GI side effects from oral iron is to switch from every day administration to every other day. This is an excellent strategy for the iron deficiency that often occurs during the first trimester of pregnancy. In fact, a study by Stoffel and colleagues published in *Lancet Haematology* in 2017 reported that administering iron every other day is associated with increased absorption compared with daily or twice-daily doses. These clinical data corroborate those from a high-quality study by Moretti and colleagues, published in *Blood* in 2015, which reported increased serum hepcidin levels after the ingestion of oral iron that decreases absorption.

It is also reasonable to take oral iron during the second trimester of pregnancy if the hemoglobin level is at least 10 g/dL. However, anyone in the third trimester of pregnancy or whose hemoglobin is less than 10 g/dL during the second trimester should receive IV iron to ensure that enough iron gets to the fetus. High-quality epidemiologic data report inadequate iron delivery to the fetus if the mother is severely iron deficient. Furthermore, a 2012 study by Congdon in the *Journal of Pediatrics* showed that infants who are born iron-deficient have a statistically significant increase in both cognitive and behavioral abnormalities. These abnormalities persist even after oral iron repletion, and are measurable with neurophysiologic correlates of cognition and concentration up to age 19 years. It is noteworthy that in the United States and most of the Western world, infants are not screened for iron deficiency.

For those who have undergone bariatric surgery and are iron deficient, 2013 guidelines from the American Society for Metabolic and Bariatric Surgery recommend oral iron as frontline treatment. My own opinion—which

is shared by many of my colleagues in this field—is that oral iron should never be used in these patients. It is largely ineffective in this situation because of the inability of iron to be conjugated to vitamin C, amino acids, and sugars in the presence of gastric acid. Normal conjugation is necessary to protect the iron as it passes through the proximal duodenum from massive alkaline secretions from the pancreas that occur as part of normal digestion. Absent that, the iron is converted to ferric hydroxide—rust—which is unabsorbable. Further, oral iron often causes significant GI side effects in a population already rife with GI perturbation. Supporting this position is a 2014 paper by Gesquiere and colleagues in *Obesity Surgery*, which reported that more than 70% of bariatric surgery patients have iron deficiency anemia even after oral iron repletion. As a result, I use IV iron as frontline therapy for all patients after bariatric surgery. The increased energy and performance are needed to maintain energy for exercise in individuals who have made such a dramatic life change to manage their obesity. I take the same approach in women with heavy uterine bleeding, in whom oral iron is unable to keep up with iron losses.

> We have much more information supporting the safety of intravenous iron.

Oral iron continues to be frontline therapy in the United States in IBD, whereas IV iron is frontline therapy for these patients in Europe. Again, I recommend upfront IV iron because oral iron is directly toxic to the intestinal epithelium. High-quality evidence published in *Gut* in 2015 suggests that oral iron negatively alters the gut microbiome, leading to intestinal inflammation. As a result, I never give oral iron to patients with IBD.

IV iron clearly should be used as frontline treatment in angiodysplasia because of oral iron's inability to keep up with losses. It also should be used in anyone with a concomitant comorbidity, because IV iron is able to bypass the hepcidin block (iron-restricted erythropoiesis). Corroborating this recommendation is that when IV iron is added to the treatment paradigm for anemia associated with chemotherapy or chronic kidney disease, the dose of the erythropoiesis-stimulating agent is nearly always decreased.

H&O How has treatment evolved over the past few years?

MA Several changes have occurred over the past few years. First, we have much more information supporting the safety of IV iron. Serious adverse events with IV iron became vanishingly rare after the removal of high-molecular-weight iron dextran from the pharmacopoeia. Minor infusion reactions, which are more likely in people who have asthma or multiple drug allergies, occur in just 1% to 3% of cases. This is based on a huge amount of published evidence constituting millions of doses of IV iron in dialysis patients.

Second, a course of IV iron used to require 5 or more individual treatment sessions, but now 4 IV iron formulations are available that allow a replacement dose of iron in 15 to 60 minutes. The need to give multiple doses of iron sucrose or ferric gluconate is obviated by the new drugs—low-molecular-weight iron dextran (INFeD, Allergan), ferumoxytol (Feraheme, AMAG Pharmaceuticals), ferric carboxymaltose (Injectafer, Daiichi Sankyo), and in Europe only, iron isomaltoside (Monofer, Pharmacosmos). Many reputable institutions continue to use a series of infusions, but I believe that a single infusion is the safest, most convenient, and most cost-effective option.

H&O What are the advantages and disadvantages of oral iron?

MA The advantages of oral iron are that it can be purchased easily, is very inexpensive, and is easy to swallow. The disadvantages are that it is frequently ineffective—it cannot keep up with active blood loss—and it causes side effects. In a study by Tolkien and colleagues that was published in *PLoS One* in 2015, 70% of patients taking ferrous sulfate experienced significant GI side effects.

H&O What are the differences among the various types of oral iron?

MA With the exception of timed-release oral iron, which is not absorbed, no study has shown the superiority of one oral iron agent over another.

H&O What are the advantages and disadvantages of IV iron?

MA The disadvantages are that it needs to be given intravenously, and it can cause infusion reactions. These reactions are rare but when they occur, they are easy to manage and often resolve without treatment. There is also a risk of staining of the skin with extravasation, clearly supporting a single infusion over multiple doses of iron sucrose or ferric gluconate. The advantages are that the treatment is all over in 15 to 60 minutes instead of 12 to

Table. Intravenous Iron Products Used in Adults

- Ferric carboxymaltose
- Ferric gluconate
- Ferumoxytol (available in the United States only)
- Iron dextran, low-molecular-weight
- Iron isomaltoside (not available in the United States)
- Iron sucrose

18 months. Patients do not experience GI toxicity, the adherence rate is 100%, and the treatment always works.

H&O What are the differences among the various types of IV iron?

MA Iron sucrose and ferric gluconate are iron salts (Table). They work effectively and are very safe but they have a less-complex carbohydrate core than the other forms of iron, so they bind the elemental iron much less tightly. No more than 200 to 250 mg should be given in a single sitting, as shown in a 2001 article by Chandler and Macdougall in the *American Journal of Kidney Diseases*.

The carbohydrate core of low-molecular-weight iron dextran is much more complex. At our center, we have treated more than 9000 patients with an infusion of 1 g in 1 hour without a single serious adverse event. We do have minor infusion reactions, but they are self-limiting, resolve without treatment, and are easy to deal with if you know what to do. No patients have been hospitalized or have developed residual toxicity.

The newer agent ferumoxytol is approved as a 510-mg, 15-minute infusion that is given in 2 doses, 3 to 8 days apart. We have shown, however that a single 1020-mg dose can be given in 15 minutes just as safely and effectively as the lower dose. Some insurance providers have already begun to reimburse for the 1020-mg infusion.

Ferric carboxymaltose is another excellent IV formulation, and the most expensive of the IV iron formulations in the United States. The cost differential in Europe is far less. The only vial size available in the United States is 750 mg, which is a shame because the most common dosage in Europe is 1000 mg over 15 minutes. Adkinson and colleagues published an article in the *American Journal of Hematology* earlier this year reporting that giving a dose greater than 1000 mg is probably of no benefit. In this double-blind study, 2000 patients were randomly assigned to receive either 2 vials of ferric carboxymaltose (1500 mg) or 2 vials of ferumoxytol (1020 mg). At 5 weeks, the hemoglobin level was 0.24 g higher with ferric carboxymaltose. Therefore, it is probably more efficient to re-treat in 4 to 6 weeks rather than administer 1000 mg in a single session.

Although it is available only in Europe, iron isomaltoside is just as efficacious and safe as ferumoxytol and ferric carboxymaltose and can be given as a total dose infusion of 1 g in 15 minutes.

H&O Why would you say there is resistance to the use of IV iron?

MA The early IV irons were associated with extremely high levels of labile free iron. They were poorly tolerated and caused terrible side effects, severe hemodynamic symptoms, and even death. When iron dextran came out in the 1950s, there was a low but real risk of serious adverse events leading to anaphylaxis. This was confirmed in a study by Hamstra and colleagues published in *JAMA* in 1980. In this study, 7 of 471 iron-deficient patients experienced anaphylactoid symptoms, all of which resolved. None of the patients died or had residua. All responded to treatment. I view these as positive data, but the authors concluded that IV iron should be reserved for only those extreme circumstances when oral iron cannot be taken and iron is absolutely necessary. There is a misperception of danger regarding the incidence and nature of serious adverse events with IV iron. More importantly, the US Food and Drug Administration and the European Medicines Agency have not granted the highest level of safety to any iron formulation.

H&O When is blood transfusion needed?

MA The available guidelines state that blood transfusion is indicated when the hemoglobin level is less than 7 g/dL, or less than 8 g/dL in a cardiac patient. But in my opinion, the answer is simple—blood transfusion is indicated when it is absolutely necessary. Fatigue and dizziness are not indications for blood transfusion; I give blood to prevent shock.

H&O Are any new treatments available for iron deficiency?

MA Alternate-day oral iron is poised to be a new approach to treatment. Another formulation that is in clinical trials in Europe is iron hydroxyethyl starch, which allows a large dose to be given in a very short period. Whether there is any reason to give a dose larger than 1000 mg will require prospective studies.

H&O What research still needs to be done in this area?

MA We need to conduct a prospective trial that compares oral with IV iron during pregnancy. We also need to

conduct a trial of oral vs IV iron in patients who have had bariatric surgery. I would also like to see a prospective study comparing the hemoglobin levels achieved with 1000 mg vs 1500 mg of IV iron. Finally, I would like to see research on what happens to IV iron after it has been administered. How much of the iron goes on to transferrin, how much goes into macrophages, and how much gets delivered to the bone marrow for erythropoiesis, are all interesting questions.

Disclosure

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Suggested Readings

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