

Emerging causes of iron deficiency anemia refractory to oral iron supplementation

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Abstract

While oral iron supplementation is commonly used throughout many clinical setting, treatment with intravenous (IV) iron has historically been reserved for specific settings, such as chronic kidney disease, gynecologic issues, and anemia associated with cancer and its treatments. However, the use of IV iron has begun to gain popularity in the treatment of iron deficiency anemia (IDA) associated with two conditions that are being seen more frequently than in years past: patients who are status post gastric bypass procedure and those with inflammatory bowel disease (IBD). The Roux-en-Y procedure involves connecting a gastric pouch to the jejunum, creating a blind loop consisting of distal stomach, duodenum, and proximal jejunum that connects to the Roux limb to form a common tract. IDA occurs in 6%-50% of patients who have undergone a gastric bypass, the etiology being multifactorial. The proximal gastric pouch, the primary site of gastric acid secretion, is bypassed, resulting in a decreased ability to metabolize molecular iron. Once metabolized, most iron is absorbed in the duodenum, which is entirely bypassed. After undergoing bypass procedures, most patients significantly limit their intake of red meat, another factor contributing to post-bypass IDA. Chronic anemia occurs in approximately 1/3 of patients who suffer from IBD,

and almost half of all IBD patients are iron deficient. IBD leads to IDA through multiple mechanisms, including chronic intestinal blood loss, decreased absorption capabilities of the duodenum secondary to inflammation, and an inability of many IBD patients to tolerate the side effects of oral ferrous sulfate. In this study, we reviewed the charts of all patients who received IV iron at Sylvester Comprehensive Cancer Center/University of Miami Hospital Clinic from January 2007 to May 2012. The most common indications for IV iron were for issues related to cancer and its treatment (21.9%), IBD (20.1%), and gastric bypass (15.0%). Of the 262 patients who received IV iron, 230 received iron sucrose and 36 received iron dextran. While doses of 100, 200, 300, and 400 mg of iron sucrose were given, 100 and 200 mg were by far the most common dosages used, 122 and 120 times, respectively. The number of dosages of iron sucrose given ranged from 1 to 46, with a mean of 5.5 and a median of 4 doses. The average dose of iron dextran given was 870.5 mg, with 1000 mg being the most common dosage used. Most patients (22 of 36) who received iron dextran only received one dose. While patients with traditional indications for IV iron, such as gynecologic issues and kidney disease, still were represented in this study, we expect to see a continued increase in physicians using IV iron for emerging gastrointestinal indications, especially considering the increased safety of new low-molecular formulations.

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Key words: Anemia; Iron deficiency anemia; Intravenous iron; Gastric bypass; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Chemotherapy-associated anemia

Core tip: Decreased absorption of oral iron leading to iron deficiency is a significant cause of anemia in several patient groups, including those status post gastric

bypass surgery and those with inflammatory bowel disease. In these patients, oral iron supplementation is unlikely to correct the deficiency. Intravenous iron is a safe, effective treatment strategy for overcoming the iron deficit seen in these patients, resulting in better outcomes and improved quality of life.

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INTRODUCTION

Intravenous iron has been available for medical use for over 60 years. Traditional indications for its use include medical conditions such as inflammatory bowel disease (IBD), chronic kidney disease (CKD), chronic inflammatory arthritis, congestive heart failure, pregnancy and postpartum state, and cancer, as well as orthopedic, cardiac, colorectal, and gynecologic procedures^[1]. The development of recombinant human erythropoietin (EPO) in the late 1980's led to a renewed interest in its use as combination therapy in the setting of such conditions as CKD and malignancies. In a randomized study of 132 hemodialysis patients, the use of intravenous (IV) iron as an adjunct to EPO led to a greater increase in hemoglobin (Hgb) levels, the need for fewer doses of EPO, and less adverse effects associated with EPO use^[2].

Iron dextran can lead to both local and systemic side effects. The most commonly reported local reactions include pruritus, pain, phlebitis, and muscle necrosis^[3]. A retrospective study of patients who received IV iron for CKD compared the safety of the dextran to the sucrose preparation^[4]. A total of 979 doses of dextran and 504 of sucrose were given, with 3 minor adverse events (AEs) occurring in the dextran group and 1 in the sucrose group. No serious AEs or anaphylactic reactions were reported in either group. Another retrospective study examined 619 patients who had received IV iron over a 2 year period^[5]. Overall, there were 32 reported AEs, but no serious AEs or anaphylactic reactions. Larger retrospective studies have shown the rate of serious AEs with iron dextran to range from 0.0002% to 0.032%, with rates of serious AEs due to iron sucrose much lower^[6]. The primary reason for the increased safety of iron sucrose is likely due to the fact that iron sucrose induces less sensitivity reactions than iron dextran does. A large safety review showed that sucrose induced 3.3 allergy episodes per million doses, while dextran led to 8.7 allergy events per million doses^[7].

The Roux-en-Y procedure, the most commonly used method of gastric bypass surgeries, involves connecting a gastric pouch to the jejunum, creating a blind loop consisting of distal stomach, duodenum, and proximal

jejunum that is connected to the Roux limb to form a common tract. A retrospective study of 150 patients who received gastric bypass found that 36.8% developed anemia^[8]. The mean time from operation to the development of anemia was 20 mo. Almost 50% had a low serum iron concentration. A more recent prospective study followed 348 patients who had undergone gastric bypass for a 10 year period and found that 54% developed anemia, while 47% were iron deficient, with iron deficiency being much more common in women than in men^[9].

While the etiology of iron deficiency anemia (IDA) in this population is often multifactorial, there are three causes that are cited most commonly: avoidance of red meat, diminished gastric acid secretion, and exclusion of the duodenum^[10]. Red meat is the primary source of iron in North America, with heme accounting for two-thirds of total body iron, while molecular iron accounts for the other third^[11]. Studies, as well as common experience, have shown that after patients undergo gastric bypass they are less able to tolerate the intake of red meat. One study of 69 patients found that 39% experienced emesis as a result of eating high fiber meats^[12]. Molecular iron must be solubilized in an acidic environment before it can be absorbed^[11]. In bypass procedures, the proximal gastric pouch, the primary site of gastric acid secretion, is bypassed. In a prospective study of eight patients who underwent a gastric bypass procedure, Behrns *et al*^[13] demonstrated a marked decrease in gastric acid secretion in the stomachs of patients after they had undergone bypass, compared to pre-procedure levels. As a result of this lack of parietal cells, molecular iron is unable to get optimally metabolized. Once metabolized, most iron is absorbed at the duodenal brush border after it has been reduced from its ferric to ferrous form by ferric reductase^[14]. However, in standard Roux-en-Y procedures, the duodenum is entirely bypassed, leading to marked decreased ability to absorb iron.

Other factors that may contribute to iron deficiency include gastritis involving the gastric pouch, esophagitis, and gastric ulcers^[15]. While patients are recommended to take multivitamin supplements after undergoing gastric bypass to prevent nutritional deficiencies, patients may still be at risk for the development of IDA. In a randomized, blinded, prospective study of 56 menstruating women who had recently undergone gastric bypass, Brolin *et al*^[16] found that twice daily ferrous sulfate, at a dose of 320 mg, was able to prevent iron deficiency. However, oral iron tablets are often difficult to tolerate, especially in patients who have undergone gastric bypass procedures, and there is still no consensus on the most effective method to limit the development of iron deficiency in this population.

Current guidelines recommend that patients who have undergone a malabsorptive procedure take 40-65 mg of oral iron daily to prevent the development of iron deficiency^[17]. However, these guidelines acknowledge that patients may have difficulty tolerating oral supplementation and do not account for the fact that many patients

may be iron deficient prior to undergoing the procedure. The guidelines also state that once iron deficiency has developed, patients may be refractory to oral iron, requiring IV iron as a means to replenish their iron stores.

Anemia occurs in approximately 1/3 of patients who suffer from IBD, and almost half of all IBD patients are iron deficient^[18]. Anemia in IBD is due to a combination of chronic intestinal blood loss, decreased absorption capabilities of the duodenum secondary to inflammation, the underlying inflammatory conditions that lead to anemia of chronic disease (ACD), and an inability of many IBD patients to tolerate the side effects of oral ferrous sulfate^[18]. When patients are in an active inflammatory state secondary to their IBD, successfully treating anemia in IBD is significantly more difficult, making control of IBD paramount to the management of anemia in IBD^[19].

Several randomized trials have evaluated the efficacy of iron versus oral supplementation in anemic patients with IBD. Lindgren *et al.*^[20] randomized 91 patients with IBD and anemia to receive oral iron sulfate or IV iron sucrose for 20 wk. The IV iron group tolerated the treatment better and saw a greater amount of patients increase their Hgb by > 2 g/dL (66% to 47%), have a resolution of their anemia (16% to 41%), and reach their reference Hgb level (42% to 22%). Another study randomized 200 patients with anemia and IBD to receive IV or oral iron in a 2:1 ratio^[21]. The study met its primary endpoint, which was to prove non-inferiority of IV iron in increasing Hgb levels over a 12 week course. Of note, that rate of discontinuation of therapy due to AEs was 7.9% in the oral group compared to 1.5% in the IV group.

New guidelines recommend IV iron as first line therapy for IDA in patients with IBD. Absolute indications for the use of IV iron include a hemoglobin < 10 g/dL, intolerance or inappropriate response to oral iron supplementation, severe disease activity, use of EPO, and patient preference^[22]. IV iron leads to a more rapid and prolonged response compared to oral therapy, and is better tolerated and leads to an improved quality of life. Furthermore, recent evidence has shown that oral iron can actually have a deleterious effect in patients with IBD, including an increase in oxidative stress, disease activity, and intestinal inflammation, as well as increasing the risk of colorectal cancer, as seen in animal models^[22]. IV iron is beneficial even in cases where the anemia is attributable to ACD, which is defined as ferritin > 100 µg/L and transferrin saturation < 16% in the setting of anemia^[23].

The combination of EPO plus IV iron has been shown to be an effective method to reduce the need for blood transfusion in patients with cancer who suffer from chemotherapy-induced anemia, as well as ACD. European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend that patients receiving chemotherapy and/or radiotherapy who develop Hgb levels between 9-11 g/dL and display symptoms of anemia be considered for EPO treatment. Patients with Hgb < 9 g/dL will likely need blood transfusions, at least as initial treatment^[24].

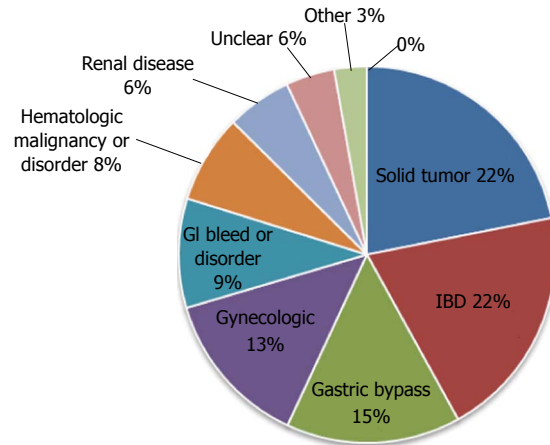


Figure 1 Indications for intravenous iron. IBD: inflammatory bowel disease; GI: Gastrointestinal.

In a randomized trial of 477 women with IDA secondary to heavy uterine bleeding, patients were randomized to receive either weekly IV iron or oral ferrous sulfate 325 mg three times a day for six weeks. Compared to those in the oral repletion group, more patients who received IV iron achieved a > 2 g/dL increase in Hgb (82% to 62%), a > 3 g/dL increase in Hgb (53% to 36%), and a correction of Hgb levels, defined as Hgb > 12 g/dL (73% to 50%), with no serious adverse effects reported in either group^[25].

RESEARCH

After obtaining approval through the University Institutional Review Board, we searched Intellidose, the electronic program that records medication administration, for all instances in which intravenous iron was administered at Sylvester Comprehensive Cancer Center/University of Miami Hospital Clinic from January 2007 to May 2012. We documented the type of iron used, number of administrations, and dosages. We then searched UChart, an electronic medical record used by the university, to ascertain the indications for IV iron based on the patients' known diagnoses.

A total of 262 patients received IV iron. Several patients had multiple indications for IV iron. The most common indications for IV iron were for issues related to cancer and its treatment (21.9%), IBD (20.1%), and gastric bypass (15.0%). Other indications included gynecologic issues (13%), a gastrointestinal bleed or disorder other than IBD (9%), and hematologic malignancies or disorders (8%) (Figure 1 and Table 1).

Of the 262 patients who received IV iron, 230 received iron sucrose and 36 received iron dextran. While doses of 100, 200, 300 and 400 mg of iron sucrose were given, 100 and 200 mg were by far the most common dosages used, 122 and 120 times, respectively. The number of dosages of iron sucrose given ranged from 1 to 46, with a mean of 5.5 and a median of 4 doses. The average dose of iron dextran given was 870.5 mg, with 1000 mg

Table 1 Specific diagnoses that led to administration of intravenous iron

Gastric bypass	43
Inflammatory bowel disease (Crohn's disease, Ulcerative colitis)	58
Gastrointestinal bleed (ulcers, arteriovenous malformation, hemorrhoids, diverticulosis, Cronkhite-Canada syndrome)	16
Gastrectomy (secondary to gastric cancer, Mucosa-associated lymphoid tissue lymphoma)	5
Celiac disease	3
Pernicious anemia	1
Colectomy secondary to Familial adenomatous polyposis	1
Bulimia	1
Small bowel resection- reason unclear	1
Solid tumor (secondary to chemotherapy, due to disease infiltration/progression)	63
Gynecologic (menorrhagia, fibroids, endometriosis)	39
Hematologic malignancy (Hodgkin's, Myelodysplastic Syndrome, Post-transplant lymphoproliferative disorder, myelofibrosis, paraproteinemia, 11 follicular lymphoma, Monoclonal gammopathy of undetermined significance, Acute myeloid leukemia, Chronic myeloid leukemia)	11
Lupus Anti-Coagulant on anti-coagulation, Antiphospholipid syndrome on anti-coagulation	4
Systemic lupus erythematosus	3
Anemia of chronic disease	1
Thalassemia	1
Sickle cell trait	1
Autoimmune hemolytic anemia	1
Jehovah's witness	4
Renal disease (polycystic kidney disease, chronic kidney disease end-stage renal disease)	16
Pregnancy	1
Rheumatoid arthritis	1
Skin wounds	1
Other indication, also on warfarin	5
Unclear on review of records (some have iron deficiency anemia as a diagnosis)	12

Note: Several patients had multiple indications for IV iron; all indications noted in chart are listed above. Data for 262 patients. Patients received treatment at Sylvester Comprehensive Cancer Center in Miami and Kendall.

being the most common dosage used. Most patients (22 of 36) who received iron dextran only received one dose.

CONCLUSION

While we expect IV iron to continue to be used for traditional indications, such as CKD and conditions associated with malignancies, we also expect to see a rise in its use for emerging indications, such as in patients status post gastric bypass procedures and in patients with IBD. Our study supports this claim, as 35% of the patients who received IV iron at our institution received it for one of these two emerging indications. Large studies have demonstrated the safety of iron dextran, and iron sucrose appears to be an even safer alternative. IV iron avoids many of the downsides of oral supplementation, such as decreased GI tolerance, absorption issues, and the ability to correct the deficiency with a short course of treatments, as opposed to long-term oral repletion. IV iron in combination with EPO has also been shown to decrease the need for blood transfusions. While oral iron remains front-line therapy for IDA, we expect to see IV iron used sooner in the course of treatment for GI-related deficiencies. This issue is likely to become more important in the future, as increasing numbers of patients undergo gastric bypass procedures and the prevalence of IBD continues to rise^[26].

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