TOPIC HIGHLIGHT

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Treatment of iron deficiency anemia associated with gastrointestinal tract diseases

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Abstract

The gastrointestinal (GI) tract is a common site of bleeding that may lead to iron deficiency anemia (IDA). Treatment of IDA depends on severity and acuity of patients' signs and symptoms. While red blood cell transfusions may be required in hemodynamically unstable patients, transfusions should be avoided in chronically anemic patients due to their potential side effects and cost. Iron studies need to be performed after episodes of GI bleeding and stores need to be replenished before anemia develops. Oral iron preparations are efficacious but poorly tolerated due to non-absorbed iron-mediated GI side effects. However, oral iron dose may be reduced with no effect on its efficacy while decreasing side effects and patient discontinuation rates. Parenteral iron therapy replenishes iron stores quicker and is better tolerated than oral therapy. Serious hypersensitive reactions are very rare with new intravenous preparations. While data on worsening of inflammatory bowel disease (IBD) activity by oral iron therapy are not conclusive, parenteral iron therapy still seems to be advantageous in the treatment of IDA in patients with IBD, because oral iron may not be sufficient to overcome the chronic blood loss and GI side effects of oral iron which may mimic IBD exacerbation. Finally, we believe the choice of oral *vs* parenteral iron therapy in patients with IBD should primarily depend on acuity and severity of patients' signs and symptoms.

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INTRODUCTION

Iron deficiency anemia (IDA) is a consequence of depletion of body iron stores due to decreased iron uptake or increased iron loss/use. Body iron content is imposed by controlling its entrance into the body through the gastrointestinal (GI) system rather than by controlling its excretion. GI diseases are among the most common etiologies of IDA because the GI tract is a common site of blood loss and GI diseases may cause malabsorption of iron. Treatment of IDA may be especially cumbersome in patients with GI diseases due to relatively poor tolerability of oral iron preparations and decreased GI iron absorption. The goal of this review is to increase awareness of parenteral iron therapies in the treatment of IDA associated with GI diseases, particularly inflammatory bowel diseases (IBDs).

IRON DEFICIENCY ANEMIA

Clinical findings

Iron deficiency causes anemia through impaired heme synthesis in maturing erythrocyte precursors. In addition to typical symptoms of anemia, patients may present with pica (appetite for bizarre foods), atrophy of upper GI mucosa (glossitis, stomatitis, achlorhydria), and spooning of the nails (koilonychia). Achlorhydria may further worsen anemia by decreasing iron absorption through the GI tract. IDA is also associated with cervical esophageal webs (Plummer-Vinson syndrome), especially in elderly women[1]. Furthermore, a high prevalence of iron deficiency with or without anemia has been reported among patients with restless legs syndrome[2].

Etiology

The etiology of IDA can be broadly categorized into two: increased iron loss/use (acute/chronic blood loss, menses, blood donation, rapid growth during childhood, pregnancy) and decreased iron uptake (inadequate diet, malabsorption due to GI disease or surgery). Common etiologies of IDA stemming from GI diseases are shown in Table 1. Any hemorrhagic lesion within the GI tract may result in blood loss and iron deficiency. IDA is often the first sign of an occult GI malignancy, celiac disease, and gastritis[3,4].

Diagnosis

Although patients with IDA generally present with microcytic, hypochromic anemia, early IDA has normocytic, normochromic indices. Reticulocyte count (corresponding to red cell production) and ferritin level (corresponding to stored iron amount) are typically low in uncomplicated IDA. Serum iron levels are not helpful by themselves because they vary with time of the day[5] and due to various systemic insults. Serum ferritin concentration is an excellent indicator of body iron stores, however, ferritin is an acute phase reactant and its level may be elevated in chronic inflammatory states. Virtually all patients with serum ferritin concentrations less than 15 ng/mL are iron deficient, with a sensitivity and specificity of 59% and 99%, respectively[6]. A cutoff limit of 30 ng/mL may increase its sensitivity to 92%[7]. Transferrin iron binding capacity (ratio of iron-unbound transferrin to total transferrin) is a helpful marker in the diagnosis of IDA and is generally lower than 16% in patients with IDA. Several conditions may complicate the diagnosis of IDA such as infections, malignancies, chronic renal failure, and inflammatory conditions by falsely elevating ferritin levels. Newer assays such as soluble transferrin receptor level and reticulocyte hemoglobin (Hb) content may be helpful, although lack of reliable standards prevented these assays from becoming a routinely available test in clinical practice[8]. Although examination of the bone marrow is considered to be the best method for evaluation of body iron status, it is invasive, expensive, and operator-dependent. In addition, recent papers questioned its accuracy[9].

TREATMENT

Keeping the diverse etiology of IDA in mind, clinicians should not consider it as a simple ailment or deficiency but a sign of a potentially life-threatening disease. Therefore, the mainstay of IDA management should be identification and correction of the underlying pathology. The search for etiology should start with history, primarily directed to assess blood loss from the GI tract and due to obstetrical causes. Potentially curable GI malignancies can be found more commonly using colonoscopy than upper endoscopy[10]. However, the overall prevalence of upper GI lesions is higher than that of lower GI lesions in patients with IDA[11,12]. The initial diagnostic test (colonoscopy vs upper endoscopy) can be chosen based on findings in the history.

Red blood cell transfusions are required in hemodynamically unstable patients primarily due to acute GI bleeding. On the other hand, transfusions should be avoided in chronically anemic, hemodynamically stable patients without cardiac or pulmonary comorbidities unless the Hb level is < 7 g/dL[13] due to the potentially life-threatening side effects of transfusions as well as their cost. In case of urgency, anemia can be corrected rapidly with parenteral iron therapy in patients with uncomplicated IDA.

Furthermore, iron studies should be performed after GI bleeding resolves even in non-anemic patients since frequent bleeding may deplete body iron stores without causing explicit anemia. Iron is essential for all cells in the body; and iron replacement in non-anemic but iron deficient patients may improve quality of life[14] and cognitive function[15]; may also delay/prevent the development of IDA in patients with frequent episodes of GI bleeding such as those with IBD and angiodysplasias. Clinicians should take side effects of oral iron therapy and the frequency of patients' bleeding episodes into consideration when deciding on iron supplementation in non-anemic iron deficient patients.

Oral iron replacement

Iron stores can be replenished through oral and parenteral therapy. In asymptomatic and mildly symptomatic patients with IDA, oral iron replacement therapy has been the mainstay therapy. Various iron salts have been used, ferrous sulfate being the most common. Use of oral iron is primarily limited by its GI side effects that are mediated by non-absorbed iron. Although newer preparations were claimed to have less side effects, ferrous sulfate is still the most commonly used oral iron preparation. Accordingly, no difference in efficacy and side effect profile were found between ferrous sulfate, ferrous gluconate, and ferrous fumarate in a randomized, double blind study[16]. However, controlled-release iron preparations and polysaccharide-iron complexes were found to have fewer GI side effects than ferrous sulfate in a few randomized trials[17,18].

Ferrous sulfate is 20% elemental iron so that a 325 mg tablet contains 65 mg iron. Although conventional wisdom

Table 1 Causes of iron deficiency anemia stemming from the GI tract

Decreased iron uptake	Increased iron loss (bleeding into GI tract)
Celiac sprue	Esophagus (esophagitis and cancer)
Giardiasis	Stomach (ulcer, gastritis, cancer, vascular lesions)
Achlorhydria (due to atrophic gastritis, *H. pylori* infection…)	Small bowel (vascular lesions)
Gastrojejunostomy and other surgical techniques bypassing the duodenum where iron absorption is maximal	Large bowel (cancer, angioectasias, adenoma, colitis)
Short bowel syndrome	

GI: Gastrointestinal; *H. pylori*: *Helicobacter pylori*.

Table 2 Pros and cons of parenteral iron over oral iron therapy

Pros
Assured repletion of iron stores regardless of factors affecting iron absorption
Rapid reversal of iron deficiency
Certain or at least assessable adherence to therapy
Infrequent side effects
One-time administration (FeCarb and LMWID)
Cons
Rare lethal drug-related adverse events
Expensive
Requires facilities/staff for administration
Simply taking tablets may be more convenient for some patients

FeCarb: Ferric carboxymaltose; LMWID: Low-molecular weight iron dextran.

dictates administration of 200 mg elemental iron daily for correction of IDA, there is no rationale for using such a high dose of oral iron. Iron absorption from the GI tract is highly efficient but saturable[19]. Accordingly, Rimon *et al*[20] demonstrated that oral iron preparations at doses as low as 15 mg/d could be used to correct iron deficiency.

To avoid GI side effects and consequent non-compliance, oral iron should be started at a low dose once daily after meals then the dose can be increased at the clinician's discretion. If well tolerated, patients should attempt to take iron preparations on an empty stomach to increase iron absorption. Within 7-14 d of therapy, an increase in reticulocyte count would be expected and within 2 mo Hb level should return to normal. Oral iron replacement should be continued to replenish iron stores, usually for an additional 4 to 6 mo after Hb normalization.

Parenteral iron replacement
The parenteral route should be used for iron replacement in patients who cannot be treated adequately with oral iron supplements due to severe GI side effects, inadequate absorption, and anemia that requires urgent correction. Many clinicians have been reluctant to use parenteral iron formulations due to the infrequent, random, but rarely lethal hypersensitive reactions to high molecular weight iron dextran (HMWID) infusions. However, the incidence of severe adverse effects is lower with low molecular weight iron dextran (LMWID) and newer parenteral iron complexes. Rates of life threatening adverse drug events were reported as 0.6, 0.9, 3.3, and 11.3 per million doses of iron sucrose, iron gluconate, LMWID, and HMWID, respectively[21]. The pros and cons of parenteral over oral iron replacement are listed in Table 2.

All parenteral iron complexes consist of a ferric iron core and a stabilizing carbohydrate shell. Table 3 demonstrates the selected characteristics, administration guidelines, and side effect profiles of four parenteral iron complexes[22,23]. Following parenteral administration, the iron-carbohydrate complex is separated by the reticuloendothelial system and iron is gradually released into the circulation combining with transferrin for transport to the liver, spleen, and bone marrow. Parenteral iron is administered at a dose to restore the total iron deficit (TID) in the body. The TID is traditionally calculated by Ganzoni's formula[24]: (2.4 × body weight (kg) × [target Hb (g/dL) - observed Hb (g/dL)] + 500 mg (iron depot). However, this formula may underestimate the iron depot in males which is estimated to be 700-900 mg[25].

Iron gluconate and iron sucrose are weaker complexes than iron dextran and ferric carboxymaltose (FeCarb). Therefore, iron is released into circulation quicker and becomes readily available for erythropoiesis[26]. While early release of iron may cause a quicker response in Hb levels, it increases the risk of acute adverse events because non-bound labile iron may cause transient capillary leak syndrome leading to nausea, hypotension, tachycardia, dyspnea, and edema mimicking anaphylaxis[27]. Hence, iron gluconate and iron sucrose have lower maximal recommended single doses.

Due to the higher incidence of anaphylactic reactions associated with iron dextran, a test dose of 25 mg as slow intravenous (IV) push is required before LMWID administration. On the other hand, LMWID can be administered at higher doses enabling physicians to administer the total iron dose at one infusion. Furthermore, LMWID is less expensive compared to the other parenteral iron complexes. Iron dextran can also be administered intramuscularly, however, this is not recommended due to the incomplete absorption from the injection site and pain on injection.

FeCarb is a novel parenteral iron complex with a favorable side effect profile that can be applied at single doses up to 1000 mg per week at a high infusion speed (1000 mg IV over 15 min)[28]. However, the safety information on FeCarb is not mature and various phase III trials are underway evaluating its efficacy and safety. As of December 2009, FeCarb has not been approved by the USA Food and Drug Administration.

Table 3 Selected characteristics and dosage guidelines of parenteral iron complexes

	LMWID	Iron gluconate	Iron sucrose	FeCarb
Concentration	50 mg/mL (2 mL vial)	12.5 mg/mL (5 mL ampule)	20 mg/mL (5 mL vial)	50 mg/mL (2 mL vial)
IV injection dose	100 mg over 2-5 min	125 mg over 10 min	100 mg over 5 min	100 mg over 2 min
Direct iron donation to transferrin	1-2	5-6	4-5	1-2
Test dose required	Yes, 25 mg slow IV push	No	No	No
Maximal single dose for IV infusion	Not limited	125	500	1000
Total dose infusion	Yes, in NS over 1-6 h	No	No	No
Pregnancy category	C	B	B	N/A
Life threatening ADEs (per 10^6 doses)	3.3	0.9	0.6	N/A

LMWID: Low molecular weight iron dextran; IV: Intravenous; ADE: Adverse drug event; NS: Normal saline; N/A: Not available.

Table 4 Clinical studies comparing parenteral and oral iron therapy

Author	Intervention	Study method	*n*	Efficacy	*P*
Schröder *et al*[33]	Elemental iron 100-200 mg/d × 6 wk	Randomized	24	[1]RR: 53%	0.85
	Iron sucrose 7 mg/kg × one dose then 200 mg once-twice/wk × 5 wk		22	[1]RR: 55%	
Erichsen *et al*[34]	Elemental iron 120 mg/d × 14 d	Crossover trial with a washout period of > 6 wk	17	Mean increase in Hb: 0.2	< 0.05
	Iron sucrose 200 mg on days 1, 5, 10		17	Mean increase in Hb: 0.7	
Kulnigg *et al*[28]	Elemental iron 200 mg/d × 12 wk	2:1 (FeCarb:oral) randomization	136	Median increase in Hb: 2.8	NS
	FeCarb 1000 mg (max) weekly (× 1-3 wk)		60	Median increase in Hb: 3.7	
Gisbert *et al*[35]	Elemental iron 106 mg/d × 3-6 mo	Hb ≥ 10.0 g/dL	78	[2]RR: 89%	NS
	Iron sucrose 200 mg twice/wk × 3-6 mo	Hb < 10.0 g/dL	22	[2]RR: 77%	
Lindgren *et al*[36]	Elemental iron 200 mg/d × 20 wk	Randomized	46	[1]RR: 47%	0.07
	Iron sucrose 200 mg weekly until calculated dose reached		45	[1]RR: 66%	

[1]Increase in Hb ≥ 2.0 g/dL; [2]Complete normalization of Hb. RR: Response rate.

IRON DEFICIENCY IN INFLAMMATORY BOWEL DISEASE

IDA in IBD requires further attention because of its complex etiology and the current debate on its treatment. Anemia is thought to be the most common extraintestinal manifestation of IBD with a prevalence of 6%-74% in different study populations (higher in hospitalized patients)[29]. Anemia in IBD is multifactorial in origin and is frequently due to the combination of iron deficiency (primary cause) and anemia of chronic disease (ACD). In some cases, anemia may be drug induced (mesalazine, sulfasalazine, azathioprine, mercaptopurine) or due to folate/vitamin B12 deficiency. Iron deficiency in IBD is primarily caused by chronic blood loss through the GI tract, however, decreased iron absorption may also play a role in patients with Crohn's disease affecting the proximal small bowel. The prevalence of iron deficiency in IBD ranges from 36% to 90% depending on the definition of iron deficiency and cohort selection[30-32].

The frequent mixture of IDA and ACD in patients with IBD creates a diagnostic dilemma. Chronic inflammation increases serum ferritin and decreases serum transferrin level. As a result, the sensitivities of ferritin and iron saturation for IDA are decreased in patients with IBD. In addition to serum ferritin level and iron saturation, clinicians may use novel tests such as soluble transferrin level or a therapeutic trial of iron replacement therapy in anemic IBD patients.

The current debate on treatment of IDA in patients with IBD centers on the choice of the iron replacement route. The advantages of parenteral over oral iron replacement are thought to be:

Parenteral therapy may be more efficacious than oral supplementation because of low iron absorption from the GI tract in patients with IBD and lower compliance to the oral therapy. However, currently available data are not sufficient to reach such a conclusion. A few studies comparing the efficacy of oral and parenteral iron therapy have been published with conflicting results[28,33-36] (Table 4). Although Lindgren *et al*[36] recently concluded that IV iron therapy was more efficacious in the treatment of IDA in IBD after an intent-to-treat analysis, this study was confounded by a high discontinuation rate in the oral therapy arm (11 of 46 patients).

Persistent blood loss may exceed the capacity of intestinal absorption of iron in some patients[37]. The maximal iron absorption from intestines depends primarily on the level of body iron store and iron intake. Iron-deficient patients receiving 100 mg elemental iron/d can absorb at most 25-37.5 mg iron/d[38,39]. Since whole blood contains 0.5 mg elemental iron/mL[40], oral iron therapy may replace the iron lost in 50-75 mL of blood in the best circumstances. Therefore, clinicians should not expect oral iron therapy to correct IDA and replenish body iron stores in patients losing more than 20-30 mL blood daily. Consequently, parenteral therapy may be more useful in patients with moderate-severe active IBD.

Parenteral therapy causes an earlier increase in Hb levels[28,34]. For that reason, it is more valuable in situations where rapid correction of anemia is required such as in hemodynamically stable patients with moderately severe symptoms of anemia or those requiring an elective procedure within a few weeks.

Oral iron therapy has a high incidence of GI side effects such as epigastric pain and diarrhea that lead to discontinuation of therapy in up to 21% of patients[29]. Additionally, it is extremely difficult to differentiate these side effects from IBD exacerbation. Blackened stools by non-absorbed iron may also mimic melena and lead to unnecessary tests. On the other hand, lower doses of iron may be better tolerated and as efficacious as higher doses. Gisbert *et al*[35] recently reported a discontinuation rate of 5% and normalization of Hb concentration in 89% of IBD patients treated with 106 mg of oral elemental iron daily.

In addition to its GI side effects, oral iron may worsen IBD as a result of non-absorbed iron-mediated toxic reactive oxygen species. Accordingly, oral iron therapy was demonstrated to worsen disease activity in several rodent models at doses 100- to 1000-fold higher than the therapeutic iron dose[41-44]. In the only animal study in which the clinically therapeutic dose in humans was used, oral iron was found to increase histologic colitis scores in DSS-induced colitis in rats[45]. Furthermore, oral iron therapy was found to worsen IBD activity indices in one clinical study[34] while it improved or had no effect in other studies[35,36,46]. Irrespectively, disease activity questionnaires in IBD patients being treated with oral iron may not reflect the true disease activity but may be confounded with the GI side effects of iron.

On the other hand, oral iron therapy is less expensive, does not require additional infusion staff and infusion facilities, does not have life-threatening side effects, and may be more convenient for some patients because of logistics. We believe parenteral iron therapy is still advantageous over oral therapy in patients with IBD due to a quicker response, efficacy in severe cases, and the GI side effects of oral therapy.

Another pressing issue on iron replacement is the duration of therapy. Kulnigg *et al*[47] recently reported that anemia recurred within 10 mo of therapy cessation in 50% of anemic IBD patients whose Hb levels had normalized after IV iron sucrose and erythropoietin therapy, indicating a need for continuous iron maintenance therapy. In addition, patients with a ferritin level > 400 mg/dL at the end of replacement therapy had a longer period until they become iron deficient. Therefore, after replenishing TID, clinicians may opt to continue iron therapy at a less frequent maintenance dose or to switch to low-dose oral therapy.

Today, the widely recommended indications for use of IV iron in IBD patients with IDA are: severe anemia (defined as Hb level < 10 g/dL), need of quick recovery, intolerance to oral iron, and failure of oral iron. We agree with all of these indications with the exception of setting a definite Hb threshold. Considering the multifactorial etiology of anemia in IBD and the widely different tolerances of people to anemia, we believe that the choice of the iron administration route should primarily depend on the severity and acuity of patients' signs and symptoms. Concentrating only on the Hb level and overlooking the factors that may affect patients' tolerance to anemia such as age, cardiac and pulmonary comorbidities may blur the bigger picture and lead to over- or under-treatment. We believe symptoms such as dyspnea on mild exertion, tachycardia, severe fatigue, and ongoing gross blood loss from the GI tract should urge the clinicians to recommend first-line parenteral iron therapy to their patients with IBD and IDA.

CONCLUSION

GI diseases are one of the most common etiologies of IDA. Iron replacement should be initiated in patients with IDA and iron deficient non-anemic patients with recurrent episodes of GI bleeding. Novel parenteral iron preparations are safer than high molecular weight iron dextran and are more useful in patients with IBD primarily due to GI side effects of oral iron therapy. Finally, regardless of the route, iron therapy needs to be continued until iron stores are completely replenished. The need for maintenance therapy should be assessed in prospective trials.

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