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Clinical Investigation

Response of Iron Deficiency Anemia to Intravenous Iron Sucrose in Pediatric Inflammatory Bowel Disease

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OBJECTIVES: The objective of this retrospective study was to evaluate the safety and efficacy of intravenous iron sucrose (IS) in iron deficient children with inflammatory bowel disease (IBD) in remission.
METHODS: Electronic medical records at a university based pediatric children's hospital were searched for patients in age range 0 to 18 years with diagnosis of IBD and treatment with IS over a 1-year period. Response to IS treatment was assessed by posttreatment changes in ferritin, hemoglobin (Hb), and mean corpuscular volume (MCV). Patients with recorded symptoms of active disease were excluded from analysis of treatment response.
RESULTS: Twelve patients were identified by the search criteria, 10 with Crohn's disease (CD), 2 with ulcerative colitis (UC). Data represent 8 patients in remission, 7 with CD and 1 with UC, who received a total of 34 IS infusions. Iron sucrose was administered in cycles of 2 infusions, 2.5 to 3.5 mg/kg/dose (maximum 200 mg), 1 week apart. Mean ferritin increased from 21.4 ± 9.2 to 52.9 ± 10.1 ng/mL ($p = 0.0005$), Hb from 10.9 ± 0.4 to 11.3 ± 0.3 g/dL ($p = 0.02$), and MCV from 76.9 ± 2 to 79.4 ± 2 fl ($p = 0.006$). Iron sucrose treatment normalized ferritin in 6 of 7, Hb in 2 of 8, and MCV in 2 of 5 patients with low pretreatment levels. No adverse effects were recorded.
CONCLUSIONS: Two IS infusions of 2.5 to 3.5 mg/kg/dose (maximum 200 mg), given 1 week apart normalized ferritin levels in most pediatric IBD patients in remission without adverse effects. Further studies are needed to determine optimal dosing schedules.

INDEX TERMS: anemia, inflammatory bowel diseases, iron-deficiency, iron sucrose, pediatrics

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INTRODUCTION

Anemia is the most common systemic complication of inflammatory bowel disease (IBD). It affects up to 70% of pediatric patients[1] and tends to persist and impact quality of life regardless of disease activity.[2] Iron deficiency is the main contributor to anemia in IBD. In a recent study 70% of children with Crohn's disease (CD) and 65% of children with ulcerative colitis (UC) were iron deficient 2 years after diagnosis,[3] indicating that the problem is underdiagnosed and/or undertreated.

Current recommendations for iron supplementation in pediatric IBD emphasize oral formulations[4] but compliance is poor due to gastrointestinal side effects.[5,6] The adult literature favors the intravenous (IV) route of administration.[7] Recently both an earlier and larger role for IV iron in pediatric patients has been proposed.[8] Despite the favorable adult experience, IV iron therapy continues to be rarely used in children with IBD and the literature is sparse on this subject. One study on IV iron dextran in pediatric IBD patients reported good efficacy with a 9% frequency of hypersensitivity reactions, none of which were life-threatening.[9] Nevertheless, the reluctance to use IV iron in children with IBD persists, likely due to concerns about serious hypersensitivity reactions.

Iron sucrose (IS), the most widely used and well-studied IV iron supplement in adults with IBD[10] is a potential alternative to iron dextran. With iron sucrose adverse effects are rare, dose dependent, and thought to result from vasoactive reaction to circulating free iron rather than

anaphylaxis.[11,12] Release of free iron may occur when large doses are administered.[11] Within the recommended dosage range, IS has an excellent record of safety and efficiency in the treatment of anemia in children with chronic renal failure[13,14] and several other conditions.[5,12]

Data on response to IS are available for adults,[15] but not for children with IBD. To fill this gap, we conducted a retrospective analysis of the efficacy and safety of IS treatments in our pediatric IBD patients over a 1-year period.

METHODS

This retrospective study was conducted at the American Family Children's Hospital, University of Wisconsin School of Medicine and Public Health and was approved by the institutional review board. The primary objective was to review IS dosing regimens and treatment responses in children with IBD followed by the author at a university-based pediatric gastroenterology clinic.

Patients were identified in UW HealthLink, a web-based application within the Epic electronic health record, by matching *International Classification of Diseases, Ninth Revision* codes 555 (CD), 556 (UC), 558.9 (other and unspecified noninfectious gastroenteritis and colitis) with age range 0 to 18 years and medication orders for IS over a 1-year period. The patient list obtained was cross-checked with the divisional database for IBD patients.

Data collected included demographic information, medical history, treatment and status of patients' IBD, IS dosing schedules, adverse reactions, folate and B12 levels, pre- and posttreatment ferritin, hemoglobin (Hb), mean corpuscular volume (MCV), and C-reactive protein (CRP). Labs obtained within 2 weeks preceding the first IS infusion and at least 2, but not later than 6 weeks following the last IS infusion were considered pre- and posttreatment, respectively. C-reactive protein levels from the same periods were used to determine if ferritin levels are comparable and are not skewed by acute phase response.[7]

Ferritin <30 ng/mL was considered consistent with iron deficiency in IBD patients without evidence of active disease in accordance with the literature.[7,16] Anemia and microcytosis were defined as Hb and MCV < mean −2 SD for age.

Treatment response was analyzed from patients who were in clinical remission and had CRP levels within 1 mg/dL from the start of IS treatment to follow-up studies. Pre- and posttreatment ferritin, Hb, and MCV levels were summarized in terms of means and ± standard errors. Changes in ferritin, Hb, and MCV from pre- to posttreatment were evaluated using a paired *t*-test. Analogously, changes in the proportions of subjects with normal ferritin, Hb, and MCV were analyzed using a paired McNemar's test. Due to the small sample size, exact p-values were calculated with a network algorithm.[17] All p-values are 2-sided and $p < 0.05$ was used for defining statistical significance.

RESULTS

Twelve patients were identified by the search criteria. Subject demographic characteristics and clinical data are found in the Table.

Mean patient age was 15.4 years (range 10-18 years), 9 patients (75%) were female, 10 patients (83%) had the diagnosis of CD, and 2 (17%) had UC. Both patients with UC were females. At the time of IS infusions, patients had been on various maintenance treatments including azathioprine, methotrexate, adalimumab (Humira, AbbVie, Inc, North Chicago, IL), infliximab (Remicade, Janssen Biotech, Inc, Titusville, NJ), mesalamine, and exclusive enteral nutrition. One patient (K) had been on azathioprine at the beginning of the study period and later was switched to methotrexate due to side effects. None of the patients had B12 or folate deficiency (data not shown).

A total of 48 IS (Venofer, American Regent, Inc, Shirley, NY) infusions were administered using the following protocol: Venofer 20 mg elemental iron/mL containing the desired amount of iron was diluted in 100 mL of 0.9% normal saline. The solution was infused IV over 30 to 60 minutes. The number of infusions received by individual patients throughout the 1-year study period ranged from 2 to 8. Doses of IS per infusion ranged from 2.1 to 5 mg/kg. The maximum single IS dose allowed was 200 mg.

Nine out of 12 patients were in remission and received IS sucrose in treatment cycles consisting of 2 infusions 1 week apart (total of 36 infusions). Eight of these patients who had both pre- and posttreatment ferritin, Hb, and MCV available for comparison are included in the analysis of

Table. Individual Patient Characteristics

Patient	A	B	C	D	E	F	G	H	I	J	K	L
Age (yr)	10	12	14	15	16	16	16	16	17	17	18	18
Diagnosis	CD	CD	CD	CD	CD	CD	UC	CD	CD	CD	CD	UC
Sex	F	F	F	M	F	M	F	M	F	F	F	F
Maintenance treatment	AZA	ADA	AZA	AZA	IFX	IFX	IFX	AZA	een	AZA	AZA, MTX	MES
Total number of IS infusions	2	4	4	8	8	2	2	4	4	2	6	2
Mean IS dose per infusion (mg/kg)	5	3	2.5	3.4	2.2	3	3	3.4	3.1	2.1	2.7	3.2
Adverse reaction	none	none	none	none	none	none	none	none	none	none	none	none
Mean increase in ferritin (ng/mL)	§	13.5	13.2	28.2	§	27	45	53	28.3	§	63.3	nfd
Mean increase in Hb (g/dL)	§	0.8	0	0.4	§	0	nfd	0.5	0.8	§	0.3	1.2
Mean increase in MCV (fl)	§	1.9	2.5	1	§	2.7	nfd	0.3	2.1	§	6.4	4
Normalization of ferritin	§	*	†	*	§	*	*	*	*	§	*	nfd
Normalization of Hb	§	*	†	†	§	†	nfd	*	†	§	†	†
Normalization of MCV	§	*	*	†	§	†	nfd	‡	‡	§	‡	†

AZA, azathioprine; ADA, adalimumab; CD, Crohn's disease; EEN, exclusive enteral nutrition; IFX, infliximab; MES, mesalamine; MTX, methotrexate; nfd, no follow-up data available; UC, ulcerative colitis

* initially abnormal, corrected with treatment

† initially abnormal, not corrected with treatment

‡ normal both pre- and post-treatment

§ cells for laboratory data from patients who were excluded from analysis of therapeutic response (patients A, E, J)

treatment response. Three patients ("A", "E," and "J") had different dosing regimens, and/or had significant changes in disease activity between the time of IS treatments and follow-up labs. Patient "A" received two 5 mg/kg IS infusions 1 day apart, patient "E" received multiple 2.2 mg/kg IS infusions administered either every other day or more than 1 week apart. Patient "A" received IS shortly after diagnosis of her CD and was in remission by the time of follow-up labs with decrease in her CRP from 34 to 0 mg/dL. Patient "J" had Clostridium difficile infection and associated flare of her UC at the time of IS infusions and recovered by the time of follow up labs with decrease in CRP from 6 to 0.6 mg/dL (data not shown). To allow assessment of similar dosing schedules and avoid confounding effect of changes in inflammatory activity on ferritin levels patients "A," "E," and "J" were excluded from analysis of treatment response and the corresponding areas in the Table are shaded.

Ferritin levels increased in all patients, mean increase ranged from 13.2 to 63.3 ng/mL. Hb increased in 6 patients, and increases ranged from 0.3 to 1.2 g/dL. MCV increased in all patients following treatment with mean increases in individual patients ranging from 0.3 to 6.4 fl (Table).

Figures 1 through 3 show mean pre- and post-treatment laboratory values, percent change in laboratory values by individual patient and the percentage of patients with normal values before and after treatment. Data represent 8 patients in remission, 7 with CD and 1 with UC, who received total of 34 IS infusions.

Mean ferritin increased from 21.4 ± 9.2 to 52.9 ± 10.1 ng/mL ($p = 0.0005$; Figure 1A). In individual patients, increases in ferritin levels from baseline ranged from 32% to 643% (Figure 1B). All patients except 2 had low ferritin levels prior to treatment. Posttreatment ferritin normalized

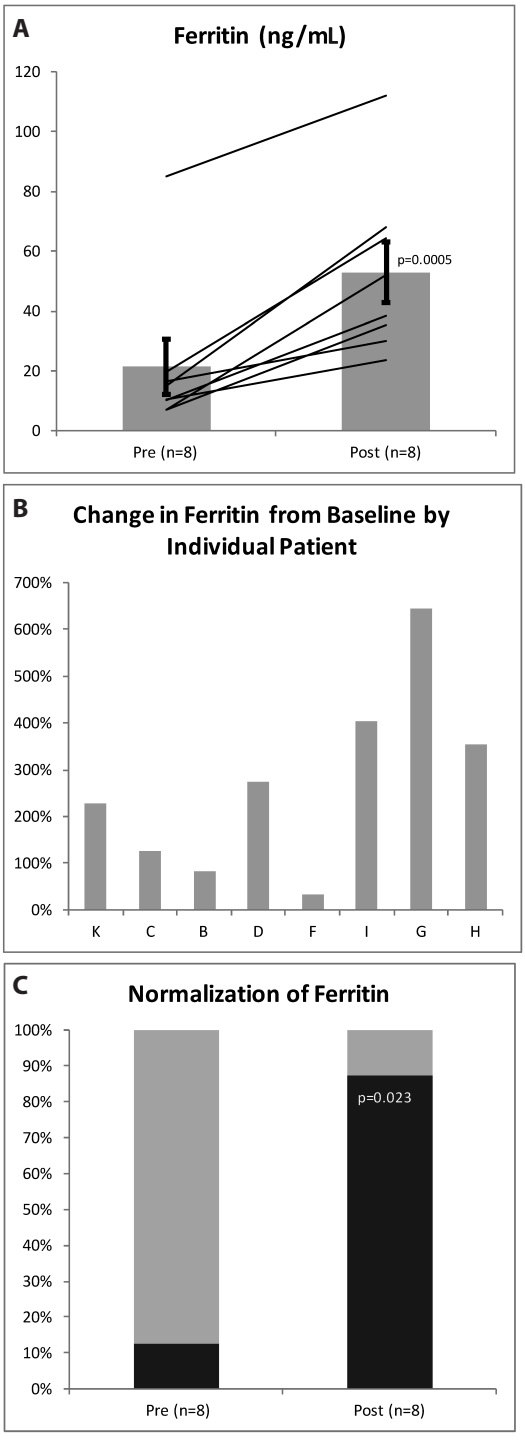

Figure 1. (A) Columns show mean ferritin level from all patients before and after iron sucrose treatments. Bars show standard error. Lines show changes in average pre- and posttreatment ferritin levels by individual patient. (B) Columns show percent changes in ferritin from baseline after treatment. (C) Darker fill in columns show percentage of patients with normal ferritin levels before (left column) and after (right column) iron sucrose treatment.

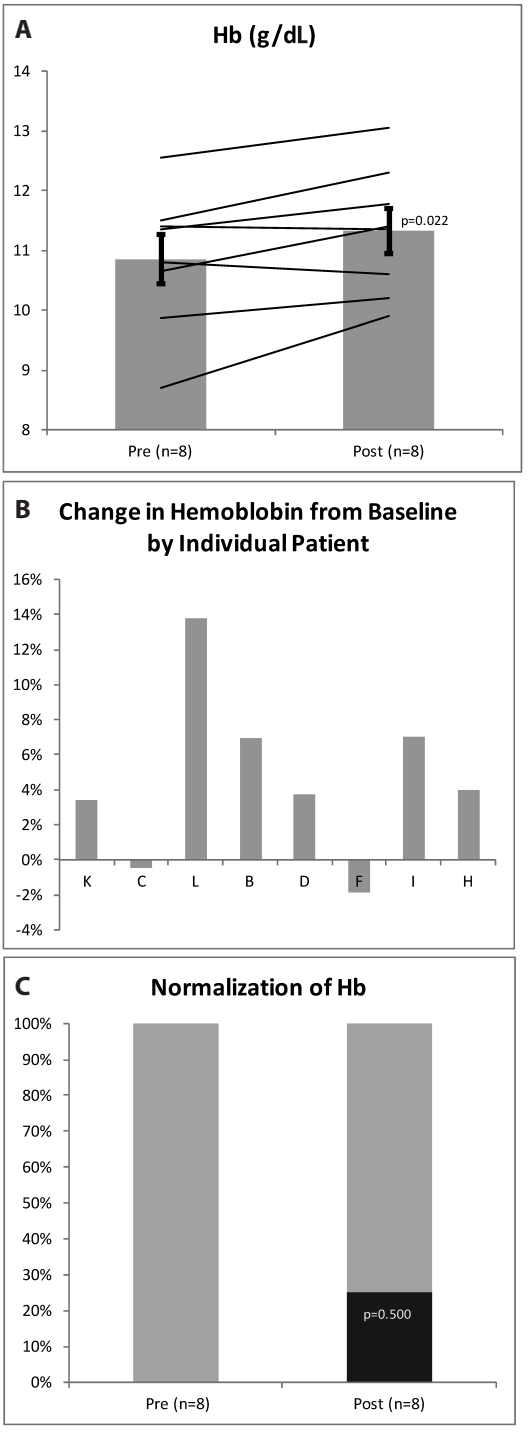

Figure 2. (A) Columns show mean hemoglobin level from all patients before and after iron sucrose treatments. Bars show standard error. Lines show changes in average pre- and posttreatment hemoglobin by individual patient. (B) Columns show percent changes in hemoglobin from baseline after treatment. (C) Darker fill in columns show percentage of patients with normal serum hemoglobin before (left column) and after (right column) iron sucrose treatment.

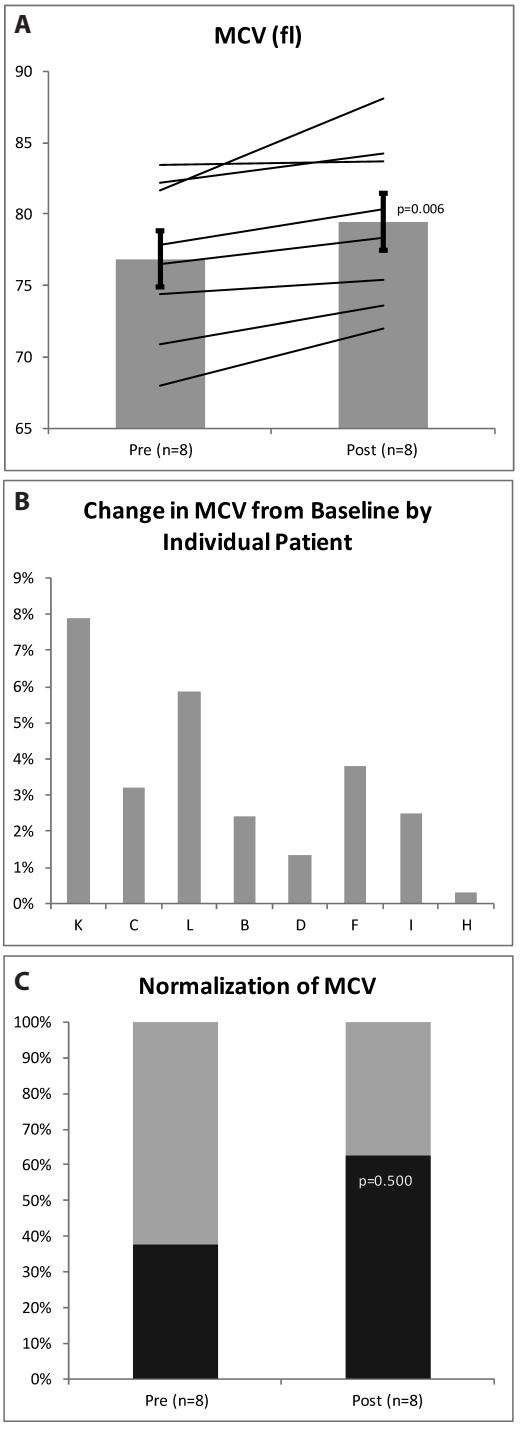

Figure 3. (A) Columns show mean mean corpuscular volume (MCV) from all patients before and after iron sucrose treatments. Bars show standard error. Lines show changes in average pre- and posttreatment MCV by individual patient. (B) Columns show percent changes in MCV from baseline after treatment. (C) Darker fill in columns show percentage of patients with normal MCV before (left column) and after (right column) iron sucrose treatment.

in all but 1 patient (p = 0.02; Figure 1C).

Mean hemoglobin increased from 10.9 ± 0.4 to 11.3 ± 0.3 g/dL (p = 0.02; Figure 2A). In individual patients increases in Hb from baseline ranged from 3.4% to 13.8%. In 2 patients, posttreatment Hb was below baseline by 0.4% and 1.9%, respectively (Figure 2B). All patients had low Hb prior to treatment. Hb normalized in 2 of 8 patients after IS treatment (p = not significant [NS]; Figure 2C).

Mean mean corpuscular volume increased from 76.9 ± 2 to 79.4 ± 2 fl (p = 0.006; Figure 3A). In individual patients, increases in MCV from baseline ranged from 0.3% to 7.8% (Figure 2B). Mean corpuscular volume was normal in 3 of 8 patients before and in 5 of 8 patients after IS treatment (p = NS; Figure 3C).

No adverse drug reactions were documented or reported with any of the 48 IS infusions. There were no clinical infections following IS treatment. Transferrin saturations remained <50% in all patients (data not shown).

DISCUSSION

To our knowledge this is the first report of IS treatment of iron deficiency anemia in children with IBD. Two doses of 2.5 to 3.5 mg/kg (up to 200 mg) IS 1 week apart significantly increased ferritin levels in children with IBD in remission. None of the patients experienced any adverse events. Anemia and microcytosis improved, but did not necessarily normalize along with ferritin, possibly in part due to confounding anemia of chronic disease.

Iron deficiency anemia has significant negative impact on quality of life, development, and cognition in children and adolescents.[2] At the same time, despite high prevalence of iron deficiency anemia[1,2] and poor compliance with oral iron supplements,[5,6] IV iron is used infrequently in pediatric IBD. In a recent survey of IS use for indications other than chronic renal failure in a large pediatric center, only 3 out of 38 patients had the diagnosis of IBD.[12]

The reluctance to use IV iron is largely related to concerns about anaphylactic reactions.[8] The stigma of risk seems to be equally attached to all IV iron formulations and the safety and ease of use of IS may not be fully appreciated by physicians caring for children with IBD. Among the IV iron preparations available in the United

States, IS was found to carry the lowest risk for hypersensitivity reactions[18] and has been found to be safe even in patients with a previous reaction to iron dextran.[19] Although our numbers are too small to draw far-reaching conclusions, our findings are in agreement with these studies on the safety of IS.

The need for multiple infusions to replace total iron deficit is a limitation of IS. Unfortunately, formulations that allow total dose IV iron infusion carry higher risk of anaphylactic reaction (iron dextran[18]) or are not approved for children (ferumoxytol, ferric carboxymaltose). In the 2 larger series on IS in children outside the chronic renal failure population,[5,12] total iron deficit was calculated by various accepted formulas also used in chronic renal failure[20,21] and replaced in doses of 5 mg/kg/dose 3 times weekly,[5] or in 7 mg/kg doses up to a maximum single dose of 300 mg every 3 to 7 days.[12] Our findings suggest that less aggressive dosage schemes could also be effective in treatment or prevention of mild to moderate iron deficiency in patients who are non-compliant with oral iron supplements. Incorporation of IS into routine management of iron deficiency would be especially easy in patients who need periodic IV access for infliximab treatment. Many of these patients are otherwise well and at risk of untreated iron deficiency anemia with deleterious effects on their quality of life and school performance. Further studies are needed to evaluate the feasibility and efficacy of this approach and determine optimal dosing.

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Abbreviations CD, Crohn's disease; CRP, C-reactive protein; Hb, hemoglobin; IBD, inflammatory bowel disease; IS, iron sucrose; IV, intravenous; MCV, mean corpuscular volume; UC, ulcerative colitis

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