


Safety and Efficacy of Intravenous Iron Sucrose for Iron-Deficiency Anemia in Children and Adolescents With Inflammatory Bowel Disease

Global Pediatric Health
Volume 6: 1–7
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DOI: 10.1177/2333794X19870981
journals.sagepub.com/home/gph


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Abstract

Background. Anemia is common in inflammatory bowel disease (IBD). Oral iron is widely used but efficacy can be reduced by poor compliance and insufficient absorption. Intravenous iron is safe and effective in adults but is not well studied in children. **Purpose.** To assess safety and efficacy of intravenous iron sucrose (IVIS) in children with IBD. **Methods.** We reviewed medical records of IBD patients <22 years of age who received IVIS at our institution between 2009 and 2014. Anemia was defined as hemoglobin (Hgb) level below normal for age and gender and iron-deficiency anemia as serum iron studies and red cell mean corpuscular volume below normal ranges. Each IVIS infusion was evaluated for safety. Efficacy was defined as ≥ 2 g/dL increase in Hgb ≤ 12 weeks from IVIS initiation. **Results.** We identified 88 patients (Crohn's disease, $n = 52$; ulcerative colitis, $n = 33$; IBD-unclassified, $n = 3$) who underwent 329 IVIS infusions over 121 courses. No patient developed anaphylaxis. Six patients developed minor adverse reactions. Of the 121 IVIS courses, 80 were included in the efficacy evaluation. There was a significant rise in Hgb (mean 9.1 ± 1.4 to 11.9 ± 1.8 g/dL; $P < .0001$, paired t test). Overall, 58.7% (47/80 courses) resulted in goal Hgb increase. **Conclusions.** IVIS is safe and effective in treating iron-deficiency anemia in pediatric IBD. There were only minor adverse events, and the observed rise in Hgb was clinically significant, with the majority achieving goal Hgb.

Keywords

intravenous iron sucrose, pediatrics, inflammatory bowel disease, anemia, iron-deficiency anemia

Received July 16, 2019. Received revised July 26, 2019. Accepted for publication July 29, 2019.

Introduction

Anemia is the most common extraintestinal manifestation in children with inflammatory bowel disease (IBD). Up to 75% of pediatric IBD patients become anemic, and 95% of IBD patients are iron deficient at diagnosis.¹⁻³ Iron-deficiency anemia (IDA) appears to be more prevalent in children than adults with IBD.^{2,4} IDA is associated with poor disease outcome and quality of life in children with IBD. Additionally, IDA has deleterious effect on growth and neurocognitive development during childhood.^{2,5,6}

Oral iron therapy is widely used in treating IDA, but patients tend to have poor compliance due to side effects, especially the gastrointestinal ones including nausea, vomiting, and abdominal pain.⁷ The optimal route of supplementation, oral versus intravenous (IV), to treat IDA in IBD patients has been a topic of debate for a long

time, mainly due to a lack of sufficient laboratory or clinical evidence to support one therapy over the other. While numerous retrospective and prospective studies in adults have demonstrated the safety and efficacy of IV iron formulations for the management of IDA in

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IBD, similar large-scale studies are lacking in pediatric IBD patients.^{8,9} Thus, the objectives of this study were to investigate the safety and efficacy of IV iron sucrose (IVIS) in children and adolescents with IBD and IDA.

Methods

Study Design

This retrospective study was conducted at University Hospitals Rainbow Babies and Children's Hospital in Cleveland, Ohio. The study was approved by our institutional review board (Institutional Review Board No. 10-14-46). Consent was waived given the retrospective nature of the study. We reviewed the inpatient and outpatient medical records of all IBD patients younger than 22 years of age at our institution between July 2009 and October 2014. IBD patients were identified through search of institutional medical records using International Classification of Diseases, Ninth Edition (ICD-9) codes (Crohn's disease [555.0-555.2 and 555.9] and ulcerative colitis [556.0-556.6 and 556.8-556.9]). The diagnosis of IBD was made by the treating gastroenterologist, based on upper endoscopy and colonoscopy findings, as well as small bowel imaging. Those who received IVIS therapy were identified by reviewing all paper and electronic medical records including notes and medication orders of those patients with IBD. Data collected included demographic information, type of IBD, blood tests results obtained prior to and after IVIS infusions (hemoglobin [Hgb]), iron level ($\mu\text{g/dL}$), mean corpuscular volume (fL), total iron-binding capacity (TIBC, $\mu\text{g/dL}$), transferrin saturation percentage (%), serum ferritin ($\mu\text{g/L}$), C-reactive protein (CRP, mg/dL), erythrocyte sedimentation rate (ESR, mm/h), and setting of IVIS infusion (inpatient or outpatient). The diagnosis of anemia was based on blood Hgb level below the normal range for age and gender. IDA was defined as hemoglobin below normal range for age and gender, and abnormalities in at least one of the following levels: serum iron level, mean corpuscular volume, TIBC, and serum ferritin. Serum ferritin levels less than 30 ng/mL were considered consistent with IDA. If there was inflammation as evidenced by an elevated CRP or ESR, serum ferritin levels of 100 ng/mL and below were considered consistent with IDA.

Each IVIS infusion was evaluated for safety (any adverse reaction). Each course consisted of 1 or more infusions according to the prescribed number of infusions based on the hematologic parameters. Response to treatment was assessed by comparing the pretreatment Hgb and repeat Hgb performed up to 12 weeks after the

first dose of IVIS. All courses were included in the safety evaluation. Courses were excluded from the efficacy analysis if they did not meet criteria for IDA or if the patient underwent packed red blood cell transfusions 30 days before or after the initiation of IVIS. Efficacy was defined as a ≥ 2 g/dL increase in Hgb level up to 12 weeks following the initiation of the IVIS course (1 or more infusions).

Statistical Analyses

Descriptive statistics for categorical variables were performed as counts and percentages, non-normally distributed continuous variables as medians and interquartile ranges (IQRs), and normally distributed continuous variables as means and standard deviations (SD). We compared the results of the initial iron studies including ferritin levels to the results of the repeat iron studies (up to 3 repeat levels) using a paired *t* test. We used univariate logistic regression to predict the response to IVIS therapy using the variables of age, gender, type of IBD, CRP, baseline transferrin saturation percentage $\leq 5\%$ versus $> 5\%$, ESR, CRP, total IVIS dose per course, dose per patient weight per course, and the setting of the IVIS infusion course. We used the 5% as a cutoff for transferrin saturation percentage because it was the median of the observed values. We performed multivariable analysis using the variables found on univariate analysis to have a *P* value $< .1$; then we adjusted for age and gender.

All analyses were presented with 95% confidence interval. Study statistical analyses were 2-tailed and completed using SPSS (IBM Corp Released 2013; IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY). A *P* value $< .05$ was considered statistically significant.

Results

We identified 88 patients with IBD (Crohn's disease, $n = 52$; ulcerative colitis, $n = 33$; and IBD-unclassified, $n = 3$) who underwent IVIS infusions during our study period. The female-to-male ratio was 1.1:1. The median age at the time of infusion was 15 years (IQR = 12-17, range = 1-21). The majority ($n = 67$) of patients received 1 course of IVIS, 14 patients received 2 courses, 3 patients received 3 courses, 3 patients received 4 courses, and 1 patient received 5 courses. A total of 121 courses of IVIS were evaluated. The median number of infusions per course was 3 (IQR = 2-3, range = 1-14 infusions). The median dose per course was 365 mg (IQR = 200-600; 7.0 mg/kg , IQR = 4.0-12.2). There

Table 1. Characteristics of the Subjects Receiving IVIS.

	No Response (n = 33 Courses)	Response (n = 47 Courses)
Age, median (IQR)	15 (13-18)	14.00 (12-16.5)
Male, n (%)	20 (60.6)	22 (46.8)
IBD, n (%)		
CD	24 (72.7)	26 (55.3)
IBD-U	0 (0.0)	1 (2.1)
UC	9 (27.3)	20 (42.6)
Number of courses (mean ± SD)	1.6 ± 0.8	1.2 ± 0.4
Single course, n (%)	20 (60.6)	39 (83.0)
Total cumulative dose (mg), median (IQR)	300 (200-540)	400.00 (200-600)
Dose (mg/kg/course), median (IQR)	6.4 (3.8-12)	7.7 (4.5-13.2)
Baseline Hgb (mean ± SD)	9.9 ± 1.1	8.6 ± 1.4
Highest Hgb within 12 weeks (mean ± SD)	10.8 ± 1.2	12.6 ± 1.6
Increase Hgb from baseline (mean ± SD)	0.9 ± 0.7	4.1 ± 1.5
CRP, n (%)		
Abnormal	16 (48.5)	27 (57.4)
Normal	7 (21.2)	13 (27.7)
N/A	10 (30.3)	7 (14.9)
ESR, n (%)		
Abnormal	16 (48.5)	33 (70.2)
Normal	3 (9.1)	4 (8.5)
N/A	14 (42.4)	10 (21.3)
Treatment location, n (%)		
Both inpatient and outpatient	5 (15.2)	7 (14.9)
Inpatient	14 (42.4)	32 (68.1)
Outpatient	14 (42.4)	8 (17.0)

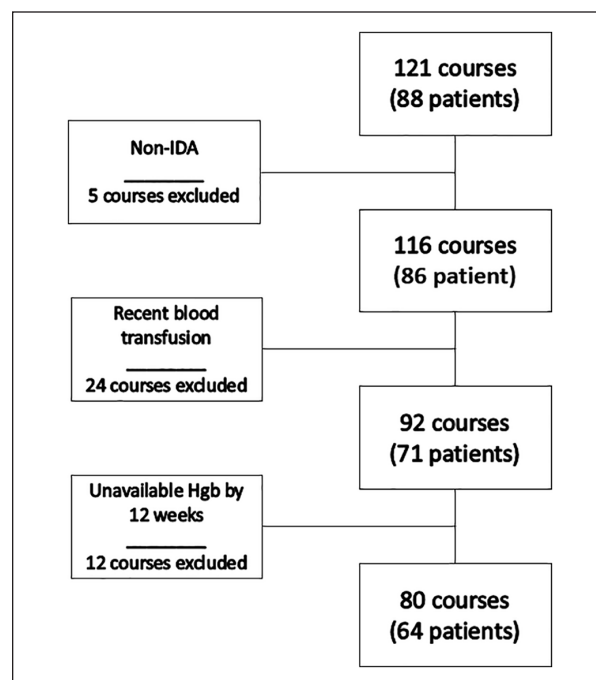
Abbreviations: IVIS, intravenous iron sucrose; IQR, interquartile range; IBD, inflammatory bowel disease; CD, Crohn's disease; IBD-U, IBD unclassified; UC, ulcerative colitis; SD, standard deviation; Hgb, hemoglobin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

were 329 IVIS infusions in total. The patient demographics are shown in Table 1.

In our cohort of patients with a total of 329 infusions, there were no episodes of anaphylaxis. Minor adverse reactions occurred during or after the IVIS infusion in 6 patients; none required discontinuation of the ongoing or future IVIS infusions. These reactions included painless edema at the IV site (n = 1), transient change in urine color (n = 2), and pain at the IV site (n = 2). There was 1 episode of thrombophlebitis requiring antibiotic therapy. This patient received additional infusions of IVIS afterward, as well as 3 other patients. The remaining 2 patients experiencing these adverse reactions did not require further IVIS infusions. No long-term adverse reactions were observed during our study.

To evaluate efficacy, we examined 121 courses. Out of the 121 courses, 41 were excluded due to a recent blood transfusion, incomplete clinical data, or absence of IDA at the time of infusion (Figure 1). Overall, there was a significant rise in Hgb from 9.1 ± 1.77 f/dL ($P = .001$, paired t test).

We examined clinical characteristics that might predict response to IVIS therapy (Table 2). On univariate analysis, 1 course versus ≥ 2 courses ($P = .029$), lower

**Figure 1.** Study overview.

Abbreviations: Hgb, hemoglobin; IDA, iron-deficiency anemia.

Table 2. Summary of Statistical Analysis.

	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	P	OR (95% CI)	P
1 course vs ≥ 2 courses	3.17 (1.13-8.89)	.029	2.99 (0.89-10.02)	.07
Age	0.95 (0.85-1.06)	.35		
Gender (male vs female)	1.75 (0.71-4.31)	.23		
Type of IBD (CD vs UC + IBD-U)	0.46 (0.18-1.21)	.12		
Baseline Hgb	0.48 (0.32-0.72)	<.0001	0.47 (0.31-0.71)	<.0001
Inpatient vs outpatient + both	2.9 (1.15-7.29)	.024	2.8 (0.95-8.17)	.06
Baseline saturation percentage ≤ 5 (n = 72)	2.9 (1.11-7.79)	.031		
Baseline iron (n = 72)	0.99 (0.94-1.04)	.73		
Baseline TIBC (n = 72)	1.002 (0.99-1.01)	.52		
Baseline ferritin (n = 62)	1.001 (0.99-1.01)	.82		
ESR (n = 56)	1.55 (0.31-7.75)	.59		
CRP (n = 63)	0.91 (0.3-2.75)	.87		
Total dose/course	1.001 (0.99-1.002)	.25		
Dose (mg/kg/course)	1.04 (0.95-1.12)	.41		

Abbreviations: OR, odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, IBD unclassified; Hgb, hemoglobin; n, number of courses out of the total 80 courses evaluated for efficacy; TIBC, total iron-binding capacity; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

baseline Hgb ($P \leq .0001$), inpatient only versus outpatient or both ($P = .024$), and transferrin saturation percentage of $\leq 5\%$ ($P = .031$) were predictors for treatment response. Age ($P = .35$), gender ($P = .23$), type of IBD ($P = .12$), and the dose of IVIS were not predictors of response. Abnormal ESR or CRP were not predictors of response (ESR, $P = .59$; CRP, $P = .87$).

Multivariable analysis with adjustment to age and gender revealed that lower baseline Hgb was the only significant predictor of response to IVIS treatment ($P \leq .0001$), while patients who received 1 course versus 2 or more courses ($P = .07$) and those who received IVIS while inpatient versus outpatient or both ($P = .06$) had results approaching significance.

Serum iron, TIBC, transferrin saturation percentage, and serum ferritin at the time of IVIS initiation were not significant predictors of response on univariate analysis. A subset of our patients had repeat iron studies. We compared the results of the available repeated iron studies to the initial ones. We found a significant rise in iron level, transferrin saturation percentage, and ferritin levels ($P \leq .0001$, .043, and .018, respectively; Table 3).

Discussion

We found that IVIS is safe and efficacious in treating IDA in pediatric IBD. In our study, there was a significant rise in Hgb of 2 g/dL or more from baseline at 12 weeks with no serious adverse events and only 6 minor adverse events. This is one of the largest studies in

children to date, encompassing 88 patients with a total of 329 infusions.¹⁰⁻¹⁴

Oral iron remains the standard of care for the management of IDA in pediatric IBD patients. However, its effectiveness is compromised by poor absorption. This is likely due, in part, to decreased transport of iron by ferroportin channels secondary to upregulation of hepcidin due to anemia of inflammation. Anemia of inflammation occurs in the context of an underlying inflammation thought to be due to a reduction in erythrocyte survival combined with impaired production of erythrocytes.¹⁵ Poor compliance secondary to high rates of gastrointestinal intolerance also adds to the suboptimal therapy. An additional concern with oral iron therapy in IBD patients derives from research using murine models of experimental colitis that suggest oral iron exacerbates the oxidative stress and alters the gut microbiota.¹⁶⁻¹⁸ Hence, it seems prudent to consider IV iron formulation as an alternative.

The adult guidelines on the diagnosis and management of IDA in IBD specifically mentions IV iron as the preferred route of supplementation based on its proven safety and efficacy profile as compared with oral iron, especially in severe anemia.^{19,20} In adult patients with IBD, there is ample evidence from well-conducted large-scale studies to suggest that IV iron is a safe and effective method for managing IDA.^{8,9,21-23} However, guidelines for the care of children with IBD do not yet make similar recommendations for IVIS.

There has been hesitance to use IV iron in pediatric IBD patients due to the concerns of serious adverse

Table 3. Changes on Repeat Iron Studies Compared With Baseline.

	First Repeat	Second Repeat	Third Repeat
Iron			
N (paired)	61	41	34
Baseline	17.8 (8.6)	18 (8.6)	17.8 (8.5)
Follow-up	48.2 (38.2)	54.5 (45.2)	49.4 (32.7)
Mean change (SD)	30.3 (37.6)	36.4 (44.3)	31.6 (34.6)
Change (%)	170%	202%	178%
95% CI	20.7-39.9	22.4-50.4	19.5-43.7
P	<.0001	<.0001	<.0001
Transferrin saturation (%)			
N (paired)	61	41	34
Baseline	6.2 (3.5)	6 (3.3)	6.1 (3.3)
Follow-up	16 (16)	16.9 (14.1)	25.7 (53.6)
Mean change	9.8 (14.9)	10.8 (13.5)	19.6 (54.3)
Change (%)	158.1%	180%	321.3%
95% CI	6-13.7	6.7-15.1	0.7-38.5
P	<.0001	<.0001	.043
Ferritin			
N (paired)	45	30	24
Baseline	36.4 (56.8)	35.1 (59.9)	31.3 (46.6)
Follow-up	75 (82.1)	73.4 (107.7)	87.2 (134.8)
Mean change	38.6 (71.4)	38.3 (82.4)	55.9 (107.3)
Change (%)	106%	109.1%	178.6%
CI 95%	17.2-60.1	7.5-69	10.6-101.2
P	.001	.017	.018

Abbreviations: SD, standard deviation; CI, confidence interval.

events, especially anaphylaxis, which was quite common when high-molecular-weight IV dextran was used.^{24,25} However, numerous IV formulations with better safety profiles have been developed. Presently, IVIS remains the most commonly used IV iron formulation in both adult and pediatric patients with robust evidence of excellent safety profile in chronic kidney disease patients undergoing hemodialysis.²⁴

Studies published on the safety and efficacy of IV iron in pediatric IBD looked at different formulations, and all have shown those formulations are safe and effective. IV iron formulations included IV iron dextran in 2 studies,^{26,27} iron ferric carboxymaltose in 2 studies,^{13,28} and IVIS in 5 studies.¹¹⁻¹⁴ The number of patients ranged from 6 patients up to 72 patients. The largest study by Stein et al¹⁴ evaluated IVIS in 72 patients, with a total of 273 infusions, demonstrating IVIS is safe and effective in children with IBD. Prior to this study, there has been no other pediatric study with more than 2 dozen patients. We evaluated a total of 329 infusions in 88 patients.

The strengths of our study is that it is one of the very few and recent studies investigating the role of IVIS in pediatric IBD patients with IDA. It is also the largest

study to date. The limitation of our study is that it is a retrospective study. We were limited by the amount of data available for evaluation. There was missing information, which limited our efficacy group data evaluation, and minor adverse events might have been missed due to poor or incomplete documentation. Also, anecdotally 1 patient developed an anaphylactic reaction after our study period ended. Our study was an exploratory study that will allow us to choose the appropriate data needed to accurately evaluate the safety and efficacy of IVIS therapy in future studies.

Conclusion

Our findings contribute to the growing evidence in support of the feasibility of using IVIS as a safe and efficacious therapy for management of IDA in pediatric IBD patients. Minor short-term and no long-term adverse events were observed during our study period. The minor adverse events did not prevent patients from getting the remaining needed infusions. The majority of our patients met the goal Hgb after the use of IVIS. Baseline Hgb was the single strong predictor of response to IVIS.

Prospective studies are needed to further evaluate the safety and efficacy of IVIS in IDA associated with pediatric IBD.

Author Contributions

R.S. and A.V. contributed to the study conception and design, data acquisition and interpretation, and drafting of the manuscript. A.M. contributed to the data interpretation & analysis. A.S.K. and S.A. contributed to the study conception and design. T.J.S. contributed to the study conception and design, data acquisition, interpretation and analysis, and drafting of the manuscript. All authors provided critical review of the manuscript and gave final approval.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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