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Safety and efficacy of a single total dose infusion (1020 mg) of ferumoxytol

Harris Khan, Paige May, Elim Kuo, Preetika Pai, Katherine Boles, Ashley McGee, Tanaka Dang and Jessica Schmit

Abstract

Purpose: Iron deficiency anemia (IDA) is the most common type of anemia. A single dose infusion of intravenous (IV) iron is a convenient treatment option. Ferumoxytol is an IV formulation of iron that is typically given in two doses of 510 mg each. Utilizing a single dose of 1020 mg over 15 min has previously been described as safe and effective. In July 2018, we began to administer a single 1020 mg dose of ferumoxytol to patients needing IV iron replacement at the North Florida/South Georgia Veterans Health System. To evaluate the impact of this change, a utilization review was conducted.

Methods: Outcomes of all patients who received ferumoxytol injections in the 6 months prior to and after the dosing strategy change were analyzed. A total of 140 patients, who received 270 separate IV ferumoxytol infusions, were included in the analysis.

Results: No significant difference in safety was observed, with one infusion reaction occurring in each group ($p = 1.00$). Efficacy also appeared equivalent with no significant difference between the change in hemoglobin for those who received a single 1020 mg dose *versus* those who received two 510 mg doses ($p = 0.764$). As expected, those who received a single total dose infusion of 1020 mg had less clinic utilization ($p < 0.0001$).

Conclusion: In summary, ferumoxytol administered as a 1020 mg single dose infusion was more convenient and should be considered a safe and effective treatment option for IDA.

Keywords: iron, iron compounds, iron-deficiency anemia, ferumoxytol

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Correspondence to:
Jessica Schmit
Department of Medicine, Division of Hematology and Oncology, Malcom Randall VA Medical Center, University of Florida College of Medicine, 1600 SW Archer Road, Gainesville, FL 32610-0277, USA
Jessica.Schmit@medicine.ufl.edu

Harris Khan
Elim Kuo
Department of Medicine, University of Florida College of Medicine, Gainesville, FL, USA

Paige May
Preetika Pai
Katherine Boles
Ashley McGee
Malcom Randall VA Medical Center, Gainesville, FL, USA

Tanaka Dang
AdventHealth East Orlando, Orlando, FL, USA

Introduction

Iron deficiency anemia (IDA) is the world's most common type of anemia, comprising 50% of cases of anemia.[1] In developed nations, iron deficiency is often secondary to chronic blood loss. Important less common causes of IDA include decreased iron absorption, usually secondary to celiac disease, proton pump inhibitors, atrophic gastritis, *Helicobacter pylori* infection or bariatric surgery.[2] Iron restricted erythropoiesis (anemia of chronic disease) is seen with many conditions including chronic renal failure, chronic heart failure, malignancies, infections, and autoimmune diseases. Although patients are not total body iron depleted, poor iron utilization in this state leads to a functional iron deficiency.[3] Treatment of iron deficiency involves both identifying and addressing the cause of iron deficiency, as well as replacing iron. There is a variety of intravenous (IV) and oral iron replacement formulations. Oral iron is widely available and relatively affordable; however, it is associated with a variety of gastrointestinal side effects, which may lead to poor adherence.[4] IV iron does not cause such effects and is more effective in patients with malabsorption syndromes or gastric surgery. It also allows for the full replacement of iron stores in a short amount of time. However, there is a risk for adverse events, including hypersensitivity reactions and in very rare cases, anaphylactic shock.[4] The cost of the drugs and need to obtain IV iron in an infusion clinic may pose an additional disadvantage for some patients.

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There are multiple different IV iron formulations, which come in the form of iron-carbohydrate complexes or colloids. The general structure consists of a spheroidal particle with iron at its center, surrounded by a carbohydrate shell which serves to stabilize the molecule and slow the release of free iron.[5] The choice of IV iron formulation is highly individualized and dependent upon product factors (i.e. infusion reaction rate and dosing frequency), patient factors (i.e. coexisting conditions and allergy history), formulary restrictions, and prescriber preference. Table 1 outlines the various available formulations of IV iron. Iron dextran was one of the earliest studied formulations. Currently, only low molecular weight iron dextran is used, as high molecular weight iron dextran has been associated with an increased number of rare but serious allergic reactions.[5] Ferric gluconate and iron sucrose both have excellent safety profiles and are frequently used. Iron sucrose is, in fact, the most widely used formulation in the world.[5] However, these two formulations consist of a smaller carbohydrate core that binds iron less tightly than dextran, resulting in significantly increased rates of free iron release. This limits the amount of iron that can be given as a single dose and thus requires multiple administrations to deliver the complete iron replacement dose. Other formulations include ferric carboxymaltose (FCM), which has been shown to be beneficial in the heart failure population,[6,7] and ferric derisomaltose (formerly iron isomaltoside), both of which are composed of iron tightly bound to a carbohydrate moiety, which decreases the risk of labile iron toxicity, enabling them to be administered as a large one-time dose.[8]

Ferumoxytol is a superparamagnetic iron oxide nanoparticle with a low molecular weight semisynthetic carbohydrate coating. It was originally developed as a contrast agent for magnetic resonance imaging (MRI) before it was recognized as an effective iron replacement strategy. Clinicians should be aware of ferumoxytol's properties as an MRI contrast agent, as the radiographic findings may appear contrast enhanced for the first 3 months after infusion. In addition, the iron particle can mimic iron overload states such as hemochromatosis.[18,22–24] It is otherwise an attractive option due to its quick administration time and low incidence of hypersensitivity reactions.

Ferumoxytol is typically given in two doses of 510 mg each. The 1020 mg dosing strategy was first described by Auerbach *et al.* in a single arm study of 60 patients treated with a single dose of 1020 mg of IV ferumoxytol and followed prospectively for safety and efficacy.[25] In 2019, Karki and Auerbach published their experience using this replacement strategy on 176 consecutive patients, finding it to be both safe and effective.[26] This dose has been described in the literature as the maximum safe dose.[27,28] A one-time dose is attractive due to the convenience of less travel and infusion visits for patients and more efficient utilization of infusion room space and staff. In July 2018, we began to administer a single 1020 mg dose of ferumoxytol as our standard IV iron replacement strategy at the North Florida/South Georgia Veterans Health System in Gainesville, Florida, USA. A retrospective chart review was conducted to evaluate the effects of this change in terms of safety, efficacy, and clinic utilization.

Methods

Data were collected on patients who received ferumoxytol between 1 February 2018 and 31 January 2019 at the North Florida/South Georgia Veterans Health System to capture approximately 6 months of data prior to, and after, a hospital-wide transition from two doses of 510 mg to a single dose of 1020 mg of IV ferumoxytol as the standard iron replacement strategy at our institution. Our primary goal was to assess safety, efficacy and clinic utilization when using a total dose infusion of 1020 mg of ferumoxytol. Prior to commencing, this project was determined to be quality assurance, as defined by the US Code of Federal Regulations.[29] Thus, it did not undergo institutional review board review or require informed patient consent. The single total dose infusion was administered over 15 min followed by nursing observation for 15–30 min.

Patients were included if they received a dose of IV ferumoxytol during the study period. Patients were excluded if they had received IV iron in the 3 months prior to the study period. Patient demographics, number and dose of iron infusions received, observed adverse reactions, and treatment response were recorded. We separated our analysis into two groups, one for safety and one for efficacy. All patients and doses of IV ferumoxytol were included in an analysis of safety. Patients were excluded from the efficacy analysis if they had received both dosing strategies (1020 mg and

Table 1. Comparison of IV iron formulations.

IV iron product	Brand name	Standard label maximum single dose	Infusion time	Recommended doses	Risk and incidence of HSRs	Average wholesale price[9]	Miscellaneous
Low molecular weight iron dextran	Cosmofer® INFeD®	1000 mg	4–6 h; 1-h infusion has also been described[10]	Multiple doses of 100 mg or single dose of 1000 mg	Highest risk[11] Any HSR: 4.7–5.6%[12,13] Mod to severe HSR: 0.7%[4]	$0.35/mg	Test dose required with 1-h observation period
Ferric gluconate	Ferrlecit®	125 mg	60 min	Multiple doses	Low risk Any HSR: 3.9%[14] Mod to severe HSR: 0.4%[14]	$1.64/mg	
Iron sucrose	Venofer®	500 mg	3.5–5 h	Multiple doses	Low risk Any HSR: 5.0%[15] Mod to severe HSRs: 0.4%[16]	$0.60/mg	
Ferumoxytol	Feraheme ® Rienso®	510 mg	15 min	Two doses given 3–8 days apart	Low risk Any HSR: 2.7%[15] Mod to severe HSRs: 0.6%[17]	$2.50/mg	MRI scans may appear contrast enhanced for up to 3 months following use[18]
Ferric carboxymaltose (FCM)	Ferinject® Injectafer®	750 mg for patients over 50 kg; 15 mg/kg for patients <50 kg	15 min	Two doses given 7 or more days apart	Low risk Any HSR: 2.1%[17,19] Mod to severe HSRs: 0.7%	$1.82/mg	Hypophosphatemia is seen in 50% of patients and can persist five weeks or more[20]
Ferric derisomaltose (formerly iron isomaltoside)	Monofer® Monoferric®	20 mg/kg, not to exceed 1500 mg	15–30 min	Single dose	Low to intermediate risk Any HSR: 8.7% Mod to severe HSRs: 0.3–66.4%[16,19]	Not available	Associated with fetal bradycardia following maternal administration[21]

HSR, hypersensitivity reaction; IV, intravenous.

510 mg) during the study period. Pre-treatment laboratory values (baseline iron saturation, hemoglobin, and ferritin) were included irrespective of the duration of time that had elapsed prior to the first infusion of IV iron. Response was assessed by recording post-treatment laboratory studies drawn within 12 weeks from infusion. If more than one value was available, the highest number was recorded for each group.

The number of visits, baseline and change in hemoglobin, ferritin and iron saturation were compared using paired *t*-tests. The rate of infusion reactions was compared using Fisher's exact test.

Results

A total of 140 patients met the criteria for analysis. Of these, 119 were included in the efficacy analysis: 59 patients who received only 510 mg doses and 60 patients who received only the 1020 mg dose. Baseline characteristics were similar between the two groups and are summarized in Table 2. The other 21 patients received both 510 mg and 1020 mg doses during the study period, and were included in the safety analysis, but not efficacy. A total of 270 separate infusions of IV iron were given during the study period (96 infusions of 1020 mg and 174 infusions of 510 mg) and were included in the safety analysis.

Efficacy was similar between the two dosing strategies as shown in Table 3. The mean increase in hemoglobin concentration was 1.96 g/dL for those who received two doses of 510 mg and 2.00 g/dL for those who received one dose of 1020 mg ($p = 0.726$). The mean increase in ferritin was also similar in the two groups, 114 ng/mL and 120 ng/mL, respectively ($p = 0.820$). The mean rise in iron saturation was 13.6% and 14.3%, respectively ($p = 0.781$). All response assessments were done within 12 weeks; two patients (one in each group) did not have a starting ferritin.

Administering the 1020 mg dose significantly reduced the number of infusion room visits required, with an average of two visits for those receiving 510 mg and one visit for those receiving 1020 mg ($p < 0.0001$).

When evaluating the infusion reaction rate, all doses of iron during the study period were included in the safety analysis ($n = 270$); 174 individual infusions of the 510 mg dose of IV ferumoxytol and 96 infusions of the 1020 mg dose of IV ferumoxytol were given during the study period. The rate of infusion reactions was not increased, with only one reaction occurring in each group: pruritis (0.57%) and nausea with vomiting (1.04%), respectively ($p = 1.00$). Both reactions were mild to moderate in nature and were managed with treatment interruption in both cases, and IV steroids in the case of pruritus. All were discharged from the infusion clinic on the same day.

Discussion

The single total dose infusion of 1020 mg of IV ferumoxytol led to a decrease in the number of infusion room visits, without significantly increasing the rate of infusion reactions or compromising efficacy, as compared to the traditional dosing of two infusions of 510 mg of ferumoxytol administered 1 to 2 weeks apart. Single dose infusion is an attractive option as it is more convenient and reduces the number of visits to the infusion room.

Many patients who receive IV iron for IDA require repeated administration due to either ongoing blood loss or chronic poor absorption. Although the risk of infusion reactions remains a concern, the risk of serious adverse effects remains very low with newer IV iron formulations.[4] The safety and efficacy among the various IV iron formulations, including low molecular weight iron dextran, ferumoxytol, ferric derisomaltose, and FCM, has been found to be comparable when administered as single infusions among a variety of settings.[4,30] Recently, ferumoxytol administered as two doses of 510 mg demonstrated non-inferiority to FCM in terms of safety and efficacy in a randomized double-blind comparison.[31] The use of IV iron may prevent the requirement for red blood cell transfusions, which is associated with a high side effect profile.[32]

The present report is the first retrospective review of its kind directly comparing the two dosing strategies of IV ferumoxytol. This review substantiates prior literature published by Auerbach *et al.* demonstrating the safety and efficacy of a single 1020 mg dose.[25] In the Auerbach study, the adverse event rate was high at 43.3%, although all reactions were mild and transient. In the present

Table 2. Baseline characteristics.

Variable	510 mg ($n=59$)	1020 mg ($n=60$)	Significance (p-value)
Age (years)			
Mean	67	64	$p=0.265$
Range	(38–92)	(25–94)	
Gender [no. (%)]			
Male	43 (72.9)	46 (76.7)	$p=0.638$
Female	16 (27.1)	14 (23.3)	
Cause of iron deficiency [no. (%)]			
Gastrointestinal bleeding	37 (62.7)	33 (55)	$p=0.192$
Heavy menses	6 (10.2)	11 (18.3)	
Poor absorptive state	0 (0)	2 (3.3)	
Unknown	16 (27.1)	14 (23.3)	
Baseline hemoglobin (g/dL)			
Mean	9.8	9.7	$p=0.726$
Range	(6.7–14.6)	(6.7–13.3)	
Distribution [no. (%)]			
<7.0	3 (5.1)	3 (5.0)	
7.1–9.0	15 (25.4)	18 (30.0)	
9.1–11.0	30 (50.8)	29 (48.3)	
>11.0	11(18.7)	10 (16.7)	
Baseline ferritin (ng/mL)			
Mean	38.2	26.2	$p=0.292$
Range	(3–415)	(4–417)	
Distribution [no. (%)]			
<30	40 (67.8)	45 (75.0)	
30–100	14 (23.7)	13 (21.6)	
100–200	2 (3.4)	0 (0)	
>200	2 (3.4)	1 (1.7)	
Not checked	1 (1.7)	1 (1.7)	
Baseline iron saturation (%)			
Mean	9.0	11.4	$p=0.216$
Range	(3–28)	(3–78)	
Distribution [no. (%)]			
<10	37 (62.7)	39 (65.0)	
10–20	20 (33.9)	16 (26.7)	
20–30	2 (3.4)	3 (5.0)	
>30	0 (0)	2 (3.3)	

Table 3. Comparison of efficacy.

Response assessment[a]	510 mg ($n = 59$)	1020 mg ($n = 60$)	Significance (p-value)
Change in hemoglobin (g/dL)			
Mean	2.0	2.0	$p = 0.764$
Range	(−0.8–5.9)	(−1.0–5.7)	
Change in ferritin (ng/mL)			
Mean	114	120	$p = 0.820$
Range	(−92–496)	(−8–1012)	
Change in iron saturation (%)			
Mean	13.6	14.3	$p = 0.781$
Range	(−14–47)	(−49–173)	

[a]Measured within 12 weeks of infusion.

review, the adverse event rate was very low (0.57% and 1.04% in 510 mg and 1020 mg arms, respectively), with only one reaction in each arm. Both events occurred during the first couple of minutes of infusion and were treated with interruption of the infusion and administration of rescue medications. Both would be classified as grade II using the Ring and Messner hypersensitivity reaction grading scale.[33] As per the revised Sampson *et al.* criteria[10] of anaphylaxis, neither patient developed anaphylaxis. Rampton *et al.* have published an excellent clinical review on the management of iron hypersensitivity reactions.[34] Our review did not follow patients after discharge from the clinic and this may have contributed to the relatively low number of adverse events in our study compared to that of Auerbach *et al.* However, the causality of such subjective adverse events happening up to 8 weeks post-discharge in Auerbach *et al.* may be difficult to establish and their significance may have been overstated. In the follow-up study published in 2019, 7.4% of patients reported minor reactions.[26]

A potential barrier to other institutions implementing a total dose infusion of ferumoxytol is the variability of medical insurance coverage of this off-label dosage. However, many major medical insurance carriers are now covering the single total dose.[26] As this review was conducted within the Veterans Health Administration, providers did not need to work with private medical insurances to gain approval for payment.

This review has several limitations. As a quality assurance project, our goal was to assess safety, efficacy, and efficiency of this dosing change. Therefore, we did not impose strict inclusion criteria to ensure uniformity of the population. As noted in the table of efficacy (Table 3), some of our population had a decrease in their measured iron stores after IV iron. This may have happened due to the study design. We included any baseline hemoglobin, ferritin and percentage saturation, regardless of the time that lapsed prior to the actual IV infusion. We also did not impose strict post-treatment inclusion criteria and any laboratory data collected within 12 weeks were included as response assessment. There was large heterogeneity in patients' pre-treatment and post-treatment laboratory measurements.

Our review was not targeted to specific populations, such as those with chronic kidney disease. Furthermore, we did not define iron deficiency as part of our inclusion criteria. Most of our patients met laboratory criteria for iron deficiency; however, some did not and likely did not actually need or benefit from an IV iron infusion. As practice patterns vary widely in the real-world setting, these findings are likely to be more representative of actual clinical practice data. We also did not attempt to explore factors that may have influenced results, such as the number of patients who received blood transfusions or who were receiving oral iron during the study period.

We performed our data analysis after the intervention had been performed, which may have led to bias. Our small sample size may have led to an inability to detect small differences in efficacy between the two dosing strategies. We did not detect any serious infusion reactions during manual chart review. Mild reactions were recorded when documented in the medical record. The actual rate of mild reactions may have been higher but were missed because of the study design. Because serious infusion reactions are rare, a much larger sample size would be needed to detect significant differences between the two groups in terms of safety.

Implementation of a single total dose infusion of 1020 mg of ferumoxytol was safe and effective. Administering ferumoxytol as a one-time dose reduced the number of infusion room visits without increasing infusion reactions or compromising efficacy. Ultimately, this strategy of implementing a one-time outpatient total dose infusion of 1020 mg of ferumoxytol could be considered at other institutions to improve infusion room access, patient convenience, and reduce costs.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical statement

Our study did not require ethical board approval because this was reviewed and approved as a quality improvement study.

ORCID iD

Harris Khan https://orcid.org/0000-0003-4055-4019

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