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Intravenous sodium ferric gluconate complex for pediatric inpatients with iron deficiency anemia or after acute blood loss

Abstract

Background: Iron deficiency anemia (IDA) is a frequent finding in hospitalized pediatric patients. Sodium ferric gluconate complex (SFGC) has been in use at our institution for rapid replenishment of iron in patients unable to take or tolerate oral iron.

Objective: Evaluate efficacy of SFGC, and incidence of adverse drug reactions (ADRs).

Methods: Retrospective review of SFGC infusions in hospitalized patients <18 years with IDA, or after acute blood loss between January 1st 2008 and April 20th 2015.

Results: Sixty-five inpatients received 1586 infusions in 738 courses of daily 1-3 mg/kg infusions followed by laboratory tests within 2-4 days. Mean number of infusions per course was 2.06±1.08, mean dose per course 4.6±3.1 mg/kg, and mean age was 8.43±6.64 years. 18.4% of the courses were administered to infants, and 24.4% to children 1-<7 years. The largest patient diagnoses group was gastrointestinal diseases (175 of 738, 23.7%), of those 64.6% (113) were inflammatory bowel disease. Comparing pre to post infusion values, there were significant increases in iron saturation, ferritin, reticulocyte count, and hemoglobin in all diagnoses and age groups. 85.8% of the courses were accompanied by erythropoietin injections. Those who received erythropoietin had higher reticulocyte count and lower ferritin levels compared to those who did not receive it (59.16±70.75 vs. 8.32±75.11, p=.005 and 81.61±179.01 vs. 134.84±117.87, p=.027 respectively). Two patients had transient hypotension but completed the infusions.

Conclusion: SFGC infusions rapidly improved iron studies, and induced hematopoiesis in all age and diagnoses groups, and without significant ADRs. Safety in neonates needs further examination.

Keywords: Pediatric anemia, iron deficiency anemia, Ferric gluconate, erythropoietin, intravenous iron

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Nabil Hassan MD,[1] Diann Reischman PhD,[2] Jessica Lyon MD,[3] Carissa Jacobs PharmD,[4] David Sterken MN, CPNP,[4] Brian Boville MD[4]

[1]Division of Pediatric Critical care, Department of Pediatrics, University of Illinois College of Medicine at Peoria, USA
[2]Department of Statistics, Grand Valley State University, USA
[3]Children's Hospital of Michigan, USA
[4]Helen DeVos Children's Hospital at Spectrum Health, Grand Rapids, USA

Correspondence: Nabil Hassan, M.D, Division of Pediatric Critical care, Department of Pediatrics, University of Illinois College of Medicine at Peoria, 530 NE Glen Oak Avenue, Peoria, IL 61637, USA, Tel 616-308-1992, Email hassne@uic.edu

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Introduction

Anemia commonly occurs in children. Estimates indicate 32.9% of the world population suffers from anemia,[1] with the majority being iron deficiency anemia (IDA). Up to 41% of children under age 5 worldwide were reported to be anemic.[2] In the US, the incidence of iron deficiency (ID) in young children is about 15%, and that of IDA is 2%.[3,4] Hospitalized children are frequently anemic for multiple reasons. Decreased iron intake, malabsorption, and blood losses (operative, and non-operative) all cause iron deficiency anemia (IDA). Additionally, acute and chronic inflammatory states like infections and inflammatory bowel disease (IBD), may develop a functional IDA state.[5]

Iron is an essential ingredient of hemoglobin (Hb). Severe IDA in hospitalized children may lead to compromised oxygen delivery, and hemodynamic instability. Bateman et al., reported that anemia was present on admission in 30% of pediatric ICU patients hospitalized for more than 48 hours, and an additional 40% developed anemia thereafter, with 51% requiring RBC transfusions.[6] In a point prevalence multinational report, the median pediatric ICU patient's Hb was 11.0 g/dL (IQR, 9.6-12.5 g/dL), with 14.2% of patients receiving a transfusion on study days.[7] Iron is critical in several enzymatic pathways in addition to being incorporated into hemoglobin; hence ID may have far reaching effects other than merely IDA. Cardiac function, muscle strength, cognition, memory, and immunity could be compromised, hence rapid replacement may be warranted.[8]

Oral iron in pediatric inpatients may not be a viable option due to intolerance, bowel inflammation, malabsorption, and slow mode of action. Intravenous iron bypasses those limitations. Commercially available IV iron products are made of a polynuclear iron core surrounded by carbohydrate shell for stabilization. The latter determines the rate of iron release and differentiates one preparation from another. Newer preparations cause fewer immune-mediated reactions but concerns for other toxicities exist[9]. Both Iron sucrose (Venofer, American Regent, Inc. USA), and sodium ferric gluconate complex (Ferrlecit, Sanofi-Aventis Canada Inc.) are rapid iron release formulations that have been available for two decades. Iron sucrose is approved for IDA in children over age 2, while sodium ferric gluconate complex (SFGC) is approved for those over age 6, on hemodialysis (HD) and receiving recombinant human erythropoietin (rHuEpo). SFGC iron is rapidly released by the reticuloendothelial system, and 80% is transported to the bone marrow as transferrin-bound iron within 24 hours.[9] this allows rapid replenishment of depleted stores, although repeated small doses are given to limit side effects. Hence, it is a suitable formulation inpatients with established venous access. The current FDA recommended dosage for SFGC iron therapy for HD pediatrics patients is 1.5 mg/kg of elemental iron diluted in 25 mL 0.9% sodium chloride and administered by IV infusion over 1 hour during the dialysis sessions.[10]

The Patient Blood Management Program (PBMP) at our institution assists with diagnosing and managing IDA in both inpatients and outpatients.[11] SFGC is frequently prescribed by the PBMP for

inpatients diagnosed with IDA, and for those with acute operative or non-operative blood loss. There is insufficient data on SFGC efficacy or safety in pediatric inpatients younger than 6 years with IDA.

We conducted this retrospective review to evaluate the efficacy of SFGC in rapid correction of the ID state in hospitalized children with IDA and those who developed anemia of acute blood loss, and to report any adverse drug reactions (ADRs). We hypothesized that rapid iron release may result in rapid improvement in hematological markers of IDA.

Methods

PBMP evaluation and management protocol[12]

When inpatients were assessed for ID, evaluation included complete blood count and serum iron studies. Threshold for diagnosis of ID was serum iron saturation <20%, and/or serum ferritin <50 mcg/ml. Anemia of inflammation was diagnosed if serum ferritin was elevated in the presence of anemia and low serum iron saturation.

SFGC was prescribed for pediatric inpatients if there was any of:

A- Inability to administer or failure to absorb oral iron (i.e. ileus, malabsorption, short gut, bowel obstruction, inflammatory bowel diseases), Hb<10 gm (< 12 gm/dL in neonates), and an ongoing or anticipated further decline

B- Rapid, unpredictable drop in Hb of >2 gm/dL due to acute operative or non-operative blood loss, not attributed to hemodilution irrespective of iron study values. In this situation, there is an acute state of anemia and total body iron deficit, while iron studies and red cell morphology are initially normal.

C- Inpatients with preoperative anemia in need of timely surgery.

SFGC was administered in courses of 1.5-3 mg/kg/dose/day (maximum rate 62.5 mg/hour, maximum dose 125 mg/2 hours) for 2-3 days, with a target total dose of 5-7 mg/kg. Patient monitoring included vital signs before infusion, every 15 minutes during infusion, and 30 minutes and 60 minutes post infusion. Any ADRs, were documented in the EMR. Patients were commonly prescribed an adjunct IV dose (300-600 U/kg, maximum 40,000 units) of rHuEpo to augment erythropoiesis during infusion of SFGC, per provider's discretion. Iron studies and CBC were routinely obtained prior, and 2-4 days following completion of the initial set of infusions to assess the need for further therapy.

The number of infusion courses that a patient received was based on the clinical course, and follow-up laboratory values. Infusions were discontinued if the patient received a RBC transfusion, developed ADR, lost IV access, or was discharged.

Study protocol

Following IRB approval and waiver of consent, we conducted a retrospective review of the EMR of all inpatients under age 18 at our institution between January 1st 2008 and April 20th 2015 who received at least one course of SFGC. We collected patients' demographics, diagnosis, administration documentations, laboratory values, monitoring data, and incidence of ADRs. We excluded patients 18 years of age or older, and those on continuous renal replacement therapy (CRRT) or extracorporeal life support (ECLS) while receiving SFGC. Patients with oncological disease and those on hemodialysis (HD) were also excluded as they were treated mostly on an outpatient basis. Transfusions were a primary service's decision based on clinical grounds. Primary outcome variables were changes in serum iron saturation and ferritin from pre-infusion to post-infusion. Post infusion was defined as 2-4 days after completion of an infusion set. Secondary outcome variables included changes in serum iron, Hb, MCV, reticulocyte absolute count. Other variables collected included C-reactive protein (CRP) when available, changes in blood pressure, and ADRs.

Statistical analysis

Quantitative variables are expressed as mean ± SD. Categorical variables are expressed as counts and percentages. For quantitative variables, comparisons between groups were made with independent samples t-tests or Mann-Whitney tests, while comparisons of pre and post values were made with paired t-tests or Wilcoxon signed rank tests. Categorical variables were compared using chi-square tests. Correlations between quantitative variables were measured with Spearman's rho due to scatterplots not showing linear relationships. The level of significance was set at 0.05. ADRs were summarized qualitatively.

Results

Demographics

Three hundred sixty-five patients received 738 SFGC courses of daily infusions (total of 1586 infusions). Patients without pre- and post-infusion laboratory results, and those transfused prior to obtaining post-infusion studies were included only in reporting ADRs and blood pressure changes (n=26 patients, 65 infusion sets). Mean number of infusions per course was 2.06 ±1.08, mean total dose per course was 4.62± 3.07 mg/kg, mean patients' age was 8.43±6.64 years, and mean body weight was 31.18±23.00 kg. A significant number (314 courses, 42.6%) were for children under 7 years, and the largest primary diagnoses was for gastrointestinal disorders, specifically IBD (113 courses, 15.3% of all) (Table 1).

Table 1 Characteristics of Study Population by infusion courses

	Number of Infusion courses (% of total courses)
Male	401 (45.7%)
Female	337 (54.3%)
Mean age (years)	8.43 ±6.64
Mean body Weight (kg) ± SD	31.18 ±23.00

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Table Continued...

	Number of Infusion courses (% of total courses)
Number infusions sets in patients	
< 1 year	136 (18.4%)
1 year- <7 year	178 (24.2%)
7 year -<13 year	162 (22.0%)
13 year- <18 year	261 (35.4%)
Diagnosis by system	
Gastro-Intestinal Disease	**175 (23.71%)**
-Inflammatory bowel disease	-113 of 175 (64.57%)
- Malabsorption, Ileus, Obstruction	- 44 of 175 (25.14%)
-Short Gut	-18 of 175 (10.29%)
Renal	**60 (8.13%)**
Postoperative anemia	**160 (21.68%)**
Trauma	**48 (6.5%)**
Sepsis, bacteremia	**95 (12.87%)**
Pulmonary	**98 (13.27%)**
Cardiac	**24 (3.25%)**
Central nervous system Nutritional Fe	**24 (3.25%)**
deficiency	**31 (4.2%)**
Others	**23 (3.12%)**

Sixty-five of 738 (8.8%) infusion courses (26 patients) were associated with RBC transfusions due to clinical indications. Those patients had body weight and total iron dose similar to those who were not transfused (n=673). Concomitantly with 633 of the 737 SFGC infusion sets (85.9%), rHuEpo was also administered. Incidence of transfusions in those receiving rHuEPO was not statistically different from those who did not (8.2% vs 12.6%, P=.144).

Efficacy of SFGC was evaluated by comparing iron studies and hematological values the day prior to iron infusions those 2-4 days post last infusion. Infusions associated with RBC transfusions were excluded from these comparisons (n=65), as well as a patient with erroneous values that could not be verified. Pre-infusion mean values are shown in Table 2. All irons studies and hematological values significantly increased post infusion except for CRP concentration which significantly decreased (p=.001).

Table 2 Summary of Pre-infusion and Post-infusion hematological and serum iron studies

	Number of paired samples	Pre-Infusion values Mean± SD	Post-Infusion values [a]Mean± SD	P-value (paired t-test)
Serum Iron (mcg/dL)	154	34.18±27.59	56.22±39.91	p<.001
Iron saturation (%)	142	17.58±15.79	26.70±26.26	p<.001
TIBC (mcg/dL)	145	222.26±92.49	235.34±82.65	p<.019
Ferritin (mcg/dL)	110	232.70±247.58	323.41±263.00	p<.001
Hemoglobin (g/dL)	478	8.95 ±1.63	9.69±5.96	p<.007
MCV (f/cell)	372	83.52±9.43	84.68±8.78	p<.001

Table Continued...

	Number of paired samples	Pre-Infusion values Mean± SD	Post-Infusion values [a]Mean± SD	P-value (paired t-test)
Absolute reticulocyte count	120	113.41±70.02	164.30±71.94	p<.001
Reticulocyte (%)	118	3.70±3.79	4.74±2.25	p<.005
CRP (mg/L)	84	66.06±66.28	41.43±48.55	p<.001[b]

Abbreviations: TIBC, total binding capacity; MCV, mean corpuscular volume; CRP, C-reactive protein

[a]Obtained 2-4 days after completion of an infusion course

[b]Student's t-test

When stratified by age groups, all groups were associated with significant increases in iron saturation, serum ferritin, absolute reticulocyte count, and Hb, except for iron saturation in infants under age 1 (Table 3). Infusion courses accompanied by rHuEpo administration compared to those without had a significantly lower pre-infusion mean Hb (8.9 ±1.5 gm/dL vs 9.6±2.0, p=.018), while serum iron and iron saturation were slightly higher (36.57±29.56 gm/dL vs23.36±12.33, p= .009) and (37±30% vs 12±5.95%, p=.045) respectively. There was no significant difference in other pre-infusion variables. Following SFGC infusions, those accompanied with rHuEpo administration had a lower ferritin concentration rise (81.61±179.01mcg/dL vs 134.84±117.87, p=.027), and a higher increase in absolute reticulocyte counts (59.2±70.7/dL vs 8.3± 75.1, p=.005) (Table 4). SFGC infusions resulted in similar rises in hemoglobin, absolute reticulocyte count, ferritin, and iron saturation in all diagnoses groups including all gastrointestinal diagnosis subsets.

Table 3 Changes in laboratory values from pre-infusion to 2-4 days post-SFGC Infusion in different age groups

-	Changes from Baseline to 2-4 days Post- Infusion course			
Age (years) (n= number of infusion courses)	Ferritin (mcg/L)[a]	Iron saturation (%)[b]	Hemoglobin (g/dL)[a]	Absolute reticulocyte count [a]
age < 1 year (n=136)	79.15±221.51 (p=0.048) n=33	1.05±15.84 (p=0.688) n=37	0.56±1.45 (p<0.001) n=94	58.57±85.46 (p<0.001) n=37
1 - < 7 years (n=178)	104.56±131.09 (p=0.003) n=16	13.24±16.84 (p=0.001) n=25	0.29±1.35 (p=0.018) n=123	29.84±75.45 (p=0.086) n=25
7 - < 13 years (n=162)	81.36±122.38 (p=0.003) n=25	6.06±11.74 (p=0.005) n=31	0.35±1.45 (p=0.021) n=94	42.46±63.44 (p=0.003) n=24
13 years - < 18 (n=261)	101.64±164.37 (p<0.001) n=36	10.39±21.21 (p<0.001) n=49	0.38±1.22 (p<0.001) n=166	63.97±61.43 (p<0.001) n=34

[a]Paired T-test

[b]Wilcoxon signed rank test

Table 4 Comparison of Changes in Laboratory Values [a] from Pre-infusion to 2-4 days post-infusion in those who did not receive Erythropoietin (rHuEPO) versus those who did

	Did not receive rHuEPO	Received rHuEPO	P-value
Hemoglobin (g/dL)	0.31±1.23 (n=47)	0.38±1.32 (n=429)	p=.711[b]
Serum Iron (mcg/dL)	28.86±35.85 (n=28)	20.51±40.35 (n=125)	p=.151[c]
Iron saturation (%)	11.15±14.18 (n=26)	6.73±18.48 (n=115)	p=.274[c]
TIBC (mcg/dL)	23.12±48.91 (n=26)	10.31±69.89 (n=118)	p=.439[c]
Ferritin (mcg/dL)	**134.84±117.87 (n=19)**	**81.61±179.01 (n=90)**	**p=.027[c]**
MCV (f/L)	**0.06±3.36 (n=44)**	**1.32±5.75 (n=327)**	**p=.005[c]**
Absolute reticulocyte count	**8.32±75.11 (n=19)**	**59.16±70.75 (n=99)**	**p=.005[c]**
Reticulocyte (%)	**0.17±2.22 (n=19)**	**1.56±2.13 (n=97)**	**p=.012[c]**
CRP (mg/L)	-35.18±52.81 (n=17)	-21.95±61.04 (n=67)	p=.388[c]

Data expressed as means ± SD

[a]2-4 days after completion of an infusion course

[b]Student's t-test

[c]Mann-Whitney test

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Correlation between pre-infusion CRP concentration as a marker of inflammation and post infusion variables was calculated utilizing the Spearman's rho. There were no significant correlation between pre-infusion CRP and post-infusion rise in Hb (N=144, ρ= -.029), serum iron (N=69, ρ=.10), or serum ferritin concentrations (N=63, ρ=.055) compared to pre-infusion values. However, there was a weak negative correlation between pre infusion serum CRP and post-infusion reticulocyte count rise (N=62, ρ=-.311, p=.003).

Adverse reactions

There were no significant changes in systolic, diastolic, or mean blood pressure of the entire group. However, in 2 out of 1586 infusions (0.13%) there was early (first 15 minutes) transient hypotension. Both patients were 17 years old. In one patient the SFGC infusion was held, but then resumed shortly thereafter. In the other patient, the infusion was continued while the patient's blood pressure was monitored closely. Both ADRs were classified as immediate mild hypersensitivity reaction.

Discussion

SFGC is a rapid release iron preparation that requires administration of smaller, more frequent doses than slow release preparations. Warady et al.[13] demonstrated in a small multicenter trial the efficacy SFGC infusions and rHuEpo in a cohort of pediatric outpatients (213 infusions in 23 patients) with IDA who were receiving hemodialysis. They maintained target range hemoglobin levels over the course of 12 weeks, with only one incident of mild hypotension during infusion. Data from our inpatient cohort with IDA or acute blood loss induced iron deficiency shows that SFGC infusions in courses of 2-3 small daily aliquots allowed rapid administration of a larger cumulative dose of iron, although smaller than those we have previously administered with the more expensive slow release feromoxytol iron formulation.[14] Iron studies had improved following an average of 4.62 mg/kg given over an average of 2 days. Follow up data within 2-4 days post infusion showed an early rise in both reticulocyte count and Hb concentration.

The efficacy was seen across the major diagnoses' spectrum. Patients with gastrointestinal disorders accounted for 23.7% of our study population. Those with short gut lack adequate intestinal absorptive surface, and those with malabsorption lack the ability to absorb iron. Patients with IBD (15.3% of the study population) likely have both factors, additionally inflammation may hinder iron metabolism, rendering it physiologically unavailable. All commercially available iron preparations have been effectively used in adults with IBD, and a large report on safety of both iron sucrose and SFGC had comparable incidence of side effects (1.74%, and 1.85% respectively).[15,16] To our knowledge, this is the first report on the use of SFGC in pediatric inpatients with GI disorders. Within our cohort, patients with different GI conditions showed similar and significant post infusion improvements in iron studies as well as hematological values despite their different mechanisms for developing IDA.

In our cohort, 314 of the infusions (42%) were administered to inpatients under age 7. 178 infusions (24.2%) were administered to patients 1-<7 years of age, and 136 infusions (18.4%) were in infants under age 1. All age groups experienced a significant post-infusion rise in absolute reticulocyte count, Hb and serum ferritin concentrations. Iron saturation also significantly rose, except in infants. That difference could be explained by more iron being incorporated into reticulocytes and hemoglobin compared to other age groups. Our population did not include patients with oncological disorders, on ECLS, receiving CRRT or HD, or premature babies.

Boucher et al.[17] retrospectively reviewed the use of IV iron at their large tertiary care center over a 6-year period. Excluding nephrology patients, 194 patients received 1088 infusions, 40.8% of those were inpatients, and only 27.3% of the infusions were with SFGC. The average age was 10.2 years, and 22.8% of the patients were under age 5, SFGC was used in only 30 of those infusions. Half of the population was accounted for by children with gastrointestinal disorders, mainly IBD. Of interest 20 minor ADRs were reported without specifying the iron preparation infused. The report highlights the scarcity of data on the use of the young inpatients and those with IBD.

Most of our study infusion courses were accompanied with rHuEPO injections. This practice was the result of many of our patients having ongoing acute or chronic illness which could have blunted their response for the iron infusion. In our patient population, those who received rHuEPO had a more robust response than those who did not. This was evidenced by higher reticulocyte counts, lower serum ferritin concentrations and lower iron saturations, all could be attributed to enhanced incorporation in hematopoiesis. This finding is consistent with previous reports of a complementary effect of IV iron and rHuEPO use. MacDougall et al showed in the PIVOTAL trial that a high dose (400 mg) of monthly IV iron sucrose in adults on maintenance hemodialysis achieved the study's primary endpoints and required decreased rHuEPO dosing.[18] Concomitant rHuEPO administration with SFGC was utilized in the trial by Warady et al.[13] Similarly, Ku et al administered rHuEPO to 4 pediatric patients with Recessive Dystrophic Epidermolysis Bullosa.[19] Three of them received SFGC and one received iron dextran for a mean duration of 14.5 months and all had significant improvement in hemoglobin.

Ongoing inflammation frequently occurs in hospitalized patients. Inflammatory mediators inhibit erythropoiesis in the bone marrow and trigger hepcidin release, which inhibits both iron absorption and mobilization to the bone marrow. In a multicenter study, iron sucrose infusions to adults with traumatic critical illness resulted in no hematological response but rather a rise in ferritin. Pieracci et al in a small multicenter trial, administered IV ferric carboxymaltose to critically ill adults, and found no immediate difference in transfusion requirements but a higher hemoglobin on discharge.[20] These varied results may be influenced by other factors like patient population, duration of the observation period, and iron formulation used. Conversely, erythropoietin may have a countering effect on inflammation and iron assimilation which may explain why we saw a drop in CRP and ferritin, and markedly improved hematologic indices. There are no pediatric studies examining the effect of IV iron with and without rHuEPO. In our population, some patients had ongoing inflammation from IBD or infection. A minority of them had serum CRP available before initiation of iron therapy. There was a statistically significant, but rather weak negative correlation between greater reticulocyte rise and higher initial CRP (ρ=-.311, p value=.003, Spearman's rho). Furthermore, a few patients had CRP both before and after iron infusions. Despite the concerns that iron may have pro-inflammatory effects, CRP was significantly lower following iron infusions. Both observations should be taken with caution. Measuring CRP was not a component of the PBMP practice but rather the managing service's decision, hence few data points were available. Additionally, many patients were receiving medications aimed to combat inflammation and likely contributed to the observed lower CRP. These findings can only be confirmed with a properly designed prospective trial.

Intravenous SFGC adverse drug reactions (ADR)

Allergic reactions to IV iron including SFGC preparations have been reported but are very rare.[21] Most ADRs are not classic allergic reactions, but rather complement activation-related pseudo reactions resulting in release of C3a, C5a, and mast cell activation, causing

vasodilation that could lead to hypotension, flushing, rash, wheezing, and infusion site pain. Mild reactions were reported at a rate of 1-2 /200 infusions, and severe reactions at a rate of 1 in 200,000 infusions. Mild cases may require slower or transient cessation of the infusion, while severe cases dexamethasone may be given.[22-24] During1586 infusions, no significant changes in BP, nor any other reactions were reported. However, in 2 infusions there was mild and transient early hypotension (within 15 minutes) that required no interventions other than temporary cessation of the infusion for a few minutes. Both patients continued to receive the same infusions thereafter. Due to the transient nature of the events, no specific allergy testing was performed.

SFGC solution (12.5 mg iron/ml) contains 9 mg/ml of benzyl alcohol which prompts the manufacturer to recommend not giving it to neonates. However, at the iron dose that is recommended, the alcohol content is significantly lower than the described (99mg/kg) toxic dose.[25] Nine infusions in our cohort were given to neonates due to their high probability of needing transfusions and the discomfort with administration of the original iron dextran formulation that was available at our institution at the time. No adverse manifestations were reported, although there was no specific long-term follow-up.

Conclusion

Intravenous SFGC is effective in rapid restoration of iron deficits and triggering of hematopoiesis in hospitalized pediatric patients with anemia due to ID or acute blood loss. This effect was augmented with concomitant use of rHuEPO and was observed across all diagnoses and age groups. Rare transient hypotension was seen when given by slow infusion aliquots. Its safety in neonates remains to be examined due to the benzyl alcohol potential neurotoxicity.

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