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The Intravenous Iron Formulation Sodium Ferric Gluconate Complex for Pediatric Inpatients with Iron Deficiency Anemia

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Abstract

Background: Iron deficiency anemia (IDA) is a prevalent issue among pediatric inpatients. Sodium ferric gluconate complex (SFGC) is employed at our institution for the rapid restoration of iron levels in patients who are unable to take or tolerate oral iron.

Objective: This study aims to evaluate the effectiveness of SFGC and assess the incidence of adverse drug reactions (ADRs).

Methods: A retrospective analysis was conducted, reviewing SFGC infusions administered to hospitalized patients aged under 18 with IDA or following acute blood loss. The study spanned from January 1st, 2008, to April 20th, 2015.

Results: Sixty-five inpatients received a total of 1586 infusions in 738 courses, involving daily 1-3 mg/kg infusions, followed by laboratory tests within 2-4 days. The mean number of infusions per course was 2.06±1.08, the mean dose per course was 4.6±3.1 mg/kg, and the mean age was 8.43±6.64 years. Infusions were administered to 18.4% of infants and 24.4% of children aged 1-<7 years. The largest patient diagnoses group comprised gastrointestinal diseases (175 of 738, 23.7%), with 64.6% (113) of those cases being inflammatory bowel disease. Comparing pre to post infusion values, there were significant increases in iron saturation, ferritin, reticulocyte count, and hemoglobin across all diagnoses and age groups. Erythropoietin injections accompanied 85.8% of the courses. Those who received erythropoietin had higher reticulocyte counts 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 experienced transient hypotension but completed the infusions.

Conclusion: SFGC infusions swiftly improved iron studies induced hematopoiesis across all age and diagnosis groups and demonstrated a favorable safety profile without significant ADRs. Further examination is warranted to determine the safety of SFGC in neonates.

1. Introduction

Anemia is a prevalent condition in children, with an estimated 32.9% of the global population experiencing this health issue, primarily attributed to iron deficiency anemia (IDA). It is reported that up to 41% of children under the age of 5 worldwide suffer from anemia. In the United States, the incidence of iron deficiency (ID) in young children is around 15%, and IDA occurs in 2% of cases. Hospitalized children frequently experience anemia due to factors such as reduced iron intake, malabsorption, and various causes of blood loss, both operative and non-operative. Inflammatory states, such as infections and inflammatory bowel disease (IBD), can contribute to functional IDA. Iron plays a crucial role in hemoglobin formation, and severe IDA in hospitalized children may lead to compromised oxygen delivery and hemodynamic instability. Anemia has been reported in a significant percentage of pediatric ICU patients, emphasizing the importance of addressing this issue promptly. Oral iron may not be feasible for inpatient treatment due to intolerance, bowel inflammation, malabsorption, and slow onset of action. Intravenous iron, specifically sodium ferric gluconate complex (SFGC), is an alternative to bypassing these limitations[1].

Commercially available intravenous iron products consist of a polynuclear iron core surrounded by a carbohydrate shell for stabilization, determining the rate of iron release. SFGC is a rapid iron release formulation with applications for patients over the age of 6, particularly those on hemodialysis receiving recombinant human erythropoietin (rHuEpo). The rapid replenishment of depleted iron stores makes SFGC suitable for inpatients with established venous access. The current FDA-recommended dosage for SFGC iron therapy in pediatric hemodialysis patients is 1.5 mg/kg of elemental iron diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour during dialysis sessions [2-4].

At our institution, the Patient Blood Management Program (PBMP) aids in diagnosing and managing IDA in both inpatients and outpatients. SFGC is frequently prescribed by PBMP for inpatients diagnosed with IDA or those experiencing acute blood loss, although limited data exists on the efficacy or safety of SFGC in pediatric inpatients under 6 years with IDA.

This retrospective review aims to assess the efficacy of SFGC in rapidly correcting the iron deficiency state in hospitalized children with IDA and those experiencing anemia due to acute blood loss. Additionally, we aim to report any adverse drug reactions (ADRs) associated with SFGC administration [5]. We hypothesize that the rapid release of iron will lead to a swift improvement in hematological markers of IDA.

2. Methods

2.1 PBMP Evaluation and Management Protocol

When assessing inpatients for iron deficiency (ID), the evaluation included a complete blood count and serum iron studies. The diagnosis threshold for ID was set at serum iron saturation <20%, and/or serum ferritin <50 mcg/ml. Anemia of inflammation was diagnosed when serum ferritin was elevated in the presence of anemia and low serum iron saturation [5-8].

2.2 Sodium ferric gluconate complex (SFGC) was prescribed for pediatric inpatients under the following conditions:

A. Inability to administer or failure to absorb oral iron, hemoglobin (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. This situation indicates 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. Adverse drug reactions (ADRs) were documented in the Electronic Medical Record (EMR). Patients were often prescribed an adjunct intravenous (IV) dose (300-600 U/kg, maximum 40,000 units) of recombinant human erythropoietin (rHuEpo) to augment erythropoiesis during SFGC infusion, at the provider's discretion. Iron studies and complete blood count (CBC) were routinely obtained before and 2-4 days following the completion of the initial set of infusions to assess the need for further therapy [9,10].

The number of infusions courses a patient received depended on the clinical course and follow-up laboratory values. Infusions were discontinued if the patient received a red blood cell (RBC) transfusion, developed an ADR, lost IV access, or was discharged.

2.3 Study Protocol

Following Institutional Review Board (IRB) approval and a waiver of consent, a retrospective review of the EMR was conducted for all inpatients under 18 at the institution between January 1st, 2008, and April 20th, 2015, who received at least one course of SFGC. Data collected included patients' demographics, diagnoses, administration documentation, laboratory values, monitoring data, and the incidence of ADRs. Patients aged 18 or older, those on continuous renal replacement therapy (CRRT) or extracorporeal life support (ECLS) while receiving SFGC, patients with oncological diseases, and those on hemodialysis (HD) were excluded, as they were predominantly treated on an outpatient basis. Transfusions were determined based on clinical grounds by the primary service. Primary outcome variables were changes in serum iron saturation and ferritin from pre-infusion to post-infusion (2-4 days after completion of an infusion set). Secondary outcome variables included changes in serum iron, Hb, mean corpuscular volume (MCV), reticulocyte absolute count, and other variables such as C-reactive protein (CRP) when available, changes in blood pressure, and ADRs [11].

2.4 Statistical Analysis

Quantitative variables were expressed as mean ± SD, and categorical variables as counts and percentages. Group comparisons for quantitative variables were conducted using independent samples t-tests or Mann-Whitney tests, while paired t-tests or Wilcoxon signed-rank tests were used to compare pre and post values. Chi-square tests were employed for categorical variables. Correlations between quantitative variables were measured with Spearman's rho. The significance level was set at 0.05, and ADRs were qualitatively summarized.

3. Results

3.1 Demographics

A total of 365 patients received 738 sodium ferric gluconate complex (SFGC) courses, amounting to 1586 infusions.

Patients without pre- and post-infusion laboratory results and those transfused before obtaining post-infusion studies were included only in reporting adverse drug reactions (ADRs) and blood pressure changes (n=26 patients, 65 infusion sets) [12-15].

The mean number of infusions per course was 2.06 ±1.08, the 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 were gastrointestinal disorders, specifically inflammatory bowel disease (IBD) (113 courses, 15.3% of all) (Table 1).

Table 1: 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

Sixty-five of 738 (8.8%) infusion courses (26 patients) were associated with red blood cell (RBC) transfusions due to clinical indications. Patients receiving transfusions had similar body weight and total iron dose to those who were not transfused (n=673).

Concomitantly with 633 of the 737 SFGC infusion sets (85.9%), recombinant human erythropoietin (rHuEpo) was also administered.

The incidence of transfusions in those receiving rHuEPO was not statistically different from those who did not (8.2% vs 12.6%, P=.144).

3.2 Efficacy of SFGC

Efficacy was evaluated by comparing iron studies and hematological values the day before iron infusions to those 2-4 days post the 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 iron studies and hematological values significantly increased post-infusion except for C-reactive protein (CRP) concentration, which significantly decreased (p=.001) [15,16].

When stratified by age groups, all groups were associated with significant increases in iron saturation, serum ferritin, absolute reticulocyte count, and hemoglobin (Hb), except for iron saturation in infants under age 1.

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 vs 23.36±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).

SFGC infusions resulted in similar rises in hemoglobin, absolute reticulocyte count, ferritin, and iron saturation in all diagnosis groups, including all gastrointestinal diagnosis subsets.

The correlation between pre-infusion CRP concentration as a marker of inflammation and post-infusion variables was calculated utilizing Spearman's rho. There were no significant correlations 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).

3.3 Adverse Reactions

There were no significant changes in systolic, diastolic, or mean blood pressure of the entire group.

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

	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

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 reactions.

4. Discussion

4.1 Sodium Ferric Gluconate Complex (SFGC) Efficacy

SFGC, known for its rapid iron release, demonstrated effectiveness in rapidly replenishing iron stores in pediatric inpatients with anemia due to iron deficiency or acute blood loss. The study findings align with Warady et al.'s research on pediatric outpatients receiving hemodialysis for iron deficiency anemia (IDA) and suggest that SFGC, administered in small daily aliquots, allows for a larger cumulative iron dose with significant post-infusion improvements in iron studies and hematological values. The study's average dose of 4.62 mg/kg over approximately 2 days resulted in early rises in reticulocyte count and hemoglobin concentration [17-21].

The efficacy extended across various diagnoses, with a notable proportion of patients having gastrointestinal disorders, including inflammatory bowel disease (IBD). This is particularly relevant as patients with short gut or malabsorption lack adequate intestinal absorptive surfaces, making them susceptible to iron deficiency. SFGC proved effective in pediatric inpatients with different gastrointestinal conditions, showcasing its versatility in addressing various mechanisms leading to IDA.

4.2 Pediatric Age Groups

The study included a diverse age range, and despite differences, all age groups experienced significant post-infusion improvements. While infants under age 1 showed a lesser increase in iron saturation, this can be attributed to more iron being incorporated into reticulocytes and hemoglobin in this age group. Notably, patients under age 7, including infants, exhibited a substantial rise in absolute reticulocyte count, hemoglobin, and serum ferritin concentrations.

4.3 Concomitant rHuEPO Administration

Most infusion courses were accompanied by recombinant human erythropoietin (rHuEPO) injections, reflecting the ongoing acute or chronic illnesses in the patient population. Patients receiving rHuEPO demonstrated a more robust response to SFGC, evident in higher reticulocyte counts, lower serum ferritin concentrations, and lower iron saturations. This aligns with previous reports suggesting a complementary effect of intravenous (IV) iron and rHuEPO use in achieving improved hematologic outcomes. The study's findings highlight the potential benefits of combining these therapies, potentially reducing the need for higher iron doses.

4.4 Inflammation and CRP Levels

Inflammation, common in hospitalized patients, can inhibit erythropoiesis and affect iron metabolism. The study observed a drop in C-reactive protein (CRP) levels following iron infusions, suggesting a countering effect on inflammation. However, caution is advised in interpreting these findings, as CRP measurements were not consistently available, and patients were concurrently receiving anti-inflammatory medications. A properly designed prospective trial is recommended to further investigate these observations [20].

4.5 Adverse Drug Reactions (ADRs)

No significant changes in blood pressure were noted in the overall group, indicating the safety of SFGC infusions. The incidence of ADRs was minimal, with only two cases (0.13%) of transient early hypotension, classified as mild hypersensitivity reactions. These events required temporary cessation of the infusion without subsequent complications.

4.6 Safety in Neonates

Although the SFGC solution contains benzyl alcohol, contraindicated for neonates, nine neonates in the cohort received infusions without adverse manifestations. Long-term follow-up data specific to neonates are lacking, emphasizing the need for further examination of SFGC safety in this population.

5. Conclusion

Intravenous SFGC is an effective option for rapidly restoring iron deficits and stimulating hematopoiesis in pediatric inpatients with anemia attributed to iron deficiency or acute blood loss. Its versatility across various diagnoses and age groups, coupled with a favorable safety profile, positions SFGC as a valuable tool in managing pediatric anemia, especially when administered with concomitant rHuEPO. The study emphasizes the importance of continued research, particularly in neonates, to comprehensively understand the benefits and safety of SFGC in diverse pediatric populations.

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