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Treatment with ferric carboxymaltose in stable patients with severe iron deficiency anemia in the emergency department

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Abstract

The AABB Choosing Wisely Campaign recommends "don't transfuse for iron deficiency without hemodynamic instability". However, the management of iron deficiency anemia (IDA) in the emergency department (ED) is heterogeneous and patients are often over-transfused. Intravenous iron is effective in correcting anemia and new formulations, including ferric carboxymaltose (FCM), allow the administration of high doses with low immunogenicity. The aim of this retrospective study was to analyze the management of hemodynamically stable patients aged 18–55 years with severe IDA (hemoglobin < 8 g/dL), who presented to the ED from January 2014 to July 2018. Patients who received FCM (FCM1) and those who did not receive FCM (FCM0) were compared. Efficacy and safety of FCM at follow-up were evaluated. Seventy-one subjects fulfilled the inclusion criteria (FCM0 $n=48$; FCM1 $n=23$). The mean Hb at admission was 6.6 g/dL. 40% in the FCM0 and 13% in FCM1 were transfused ($p=0.02$). 21% of FCM0 patients were admitted to the ward, while all FCM1 were discharged ($p=0.02$). Within 2 weeks, the Hb increase was 2.8 ± 1 g/dL in the FCM1 group. Sixteen FCM1 patients were evaluated at 52 ± 28 days (median 42, range 27–122): the average Hb increase was 5.3 ± 1.4 g/dL. In summary, we showed that FCM administration in the ED in hemodynamically stable patients was associated with fewer transfusions and hospital admissions compared to the FCM0 group; moreover, it succeeded in safely, effectively and rapidly increasing Hb levels after discharge from the ED. Further studies are needed to develop recommendations for IDA in the ED and to identify transfusion thresholds for non-hospitalized patients.

Keywords Severe anemia · Iron deficiency · Ferric carboxymaltose · Transfusion · Choosing wisely

Introduction

Anemia affects a third of the world population and half of the cases are due to iron deficiency (ID) [1]. Iron deficiency anemia (IDA) is considered an "outpatient" and non-urgent issue; however, patients with severe IDA (hemoglobin (Hb) < 8 g/dL) are often referred to the emergency department (ED) for acute management. Because of the lack of guidelines for IDA treatment in the ED, its management varies among physicians [2].

Treatment of anemia should be established according to the time of onset rather than its severity. Acute anemia, usually due to hemorrhage, and less frequently due to acute hemolysis, might present with hemodynamic instability, requiring blood transfusion, while in chronic anemia, compensatory mechanisms develop and patients are paucisymptomatic [3]. Few studies in adult [2], geriatric [4] and pediatric [5] ED settings show that IDA is underrecognized,

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not appropriately treated with iron and over-transfused to rapidly increase Hb levels and, if possible, discharge the patient. Of note, red blood cell (RBC) transfusion has several and potentially serious risks, including hemolytic reactions, other acute or delayed transfusion reactions, volume overload (TACO), transfusion-related lung injury (TRALI), immunodepression (TRIM) and infectious complications [6]. Moreover, allogenic blood is not an endless resource, with significant costs for health care systems and society [7].

The latest American Association of Blood Banks (AABB) Guidelines for transfusion thresholds recommend a restrictive transfusion strategy for hospitalized hemodynamically stable adults, including critically ill [8], while there are no specific recommendations for non-hospitalized patients. The Choosing Wisely Campaign of the AABB recommends "don't transfuse red blood cells for iron deficiency without hemodynamic instability" [9]. A quality improvement study reported that an improvement in red blood cell (RBC) transfusion appropriateness for IDA in the ED can be achieved and maintained with the implementation of simple educational and practical interventions. Involvement of the users (ED staff) in developing algorithms and ongoing communication between the transfusion medicine department and ED staff is key [10]. A recent Italian study by Beverina et al. showed an overall good appropriateness (74.5%) of RBC transfusion in the ED in a tertiary care hospital; however, a remarkable rate of improper red cell mass was observed in the transfused patients, and at least a part of the issued RBC could have been replaced by intravenous iron administration [11].

IDA treatment is based on the identification and control of the cause, and on iron supplementation. For severe anemia, intravenous (IV) iron is more effective, producing a faster recovery [12]. In the past, the use of IV iron was limited by the risk of free iron toxicity and immunogenicity. New IV iron formulations, ferumoxytol, iron isomaltoside and ferric carboxymaltose (FCM), allow the administration of a high dose of iron with lower risk of anaphylactic reactions [13-15]. FCM is the formulation available in our institution and it is administered in a high single dose (up to 1000 mg of iron) with rapid infusion (15 min). It has proven to be safe and rapidly effective in the treatment of anemia in several settings [16-20].

Moreover, Quintana-Diaz et al. showed that in a fast-track anemia clinic in the ED for management of sub-acute, moderate-to-severe anemia, the administration of FCM is a safe, and probably cost-effective option [21].

In 2016, FCM became available in the ED of our institution, Fondazione IRCCS Ca' Granda Ospedale Policlinico, Milan, Italy. No specific training of ED staff for the use of FCM was implemented. The aim of our study was to retrospectively analyze the management of patients aged 18–55 with severe chronic or sub-acute IDA, presenting to our ED. Then, we compared the group treated with FCM in the ED (FCM1) to that treated with other options (FCM0) in relation to frequency of RBC transfusions and hospitalizations. Moreover, our aim was to evaluate the efficacy and safety of the treatment with FCM at a short- and a long-term follow-up.

Methods

This study was approved by the Institutional Ethics Committee of our institution. Data were collected and analyzed retrospectively. We searched the database of the ED from January 2014 to July 2018 for patients with a diagnosis that included at least one of the following: anemia, transfusion, bleeding, hemorrhage, heavy menstrual bleeding, and rectal bleeding.

Inclusion criteria:

- Severe chronic or sub-acute IDA (Hb < 8 g/dL) due to chronic loss or reduced iron intake/absorption. Iron deficiency is intended as absolute iron deficiency (ferritin < 30 µg/L). Iron status evaluated within the previous 3 months was accepted. If a recent iron status was not available, the presence of a microcytic anemia in a subject with a history of IDA or history suggestive of chronic loss and/or malabsorption was considered sufficient. The remaining subjects were tested in the ED for iron status
- Age between 18 and 55 years
- Hemodynamically stable

Exclusion criteria:

- Overt bleeding (excluding menstrual bleeding)
- History of cardiovascular diseases
- Chest pain/discomfort, EKG alterations
- Concomitant acute infection
- Pregnancy
- Other reasons to hospitalize the patient
- Known hypersensitivity to IV iron
- Contraindications to IV iron administration

FCM administration

FCM was administered IV in 15–20 min, diluted in 100 ml or 250 ml of saline solution for the dose of 500 and 1000 mg, respectively.

Time point analysis of clinical and hematological parameters

- T0: admission in the ED
- T1: discharge from the ED

- T2: short-term follow-up
- T3: long-term follow-up

Statistical analysis

Differences between FCM0 and FCM1 patients' characteristics were analyzed using Chi-squared test (categorical variables) or Wilcoxon–Mann–Whitney (quantitative variables) test. The primary outcome was the transfusion need. The relative risk (RR) and 95% confidence interval (CI) of transfusion (FCM1 vs FCM0) were evaluated with a Poisson analysis with robust standard error, adjusted for gender, age (continuous), IDA history, and presence of symptoms. Statistical analyses were performed with Stata15 (StataCorp. 2017).

Results

Patient characteristics

From January 2014 to July 2018, 71 patients fulfilled the inclusion criteria and 23 were treated with FCM in the ED. Demographic, clinical and hematological characteristics at admission to the ED (T0) are described in Table 1. The FCM0 ($n=48$) and FCM1 ($n=23$) groups did not differ for age, sex, history of IDA, complained symptoms (fatigue, palpitations, pre-syncope or syncope) and hematological parameters. The most frequent cause of IDA was heavy menstrual bleeding (78%), while in the remaining patients, it was hemorroidal bleeding (13%) and malabsorption (bariatric surgery and atrophic gastritis) (9%). At admission (T0), the mean Hb was 6.7 ± 0.8 g/dL and 6.3 ± 0.9 in the FCM0 and FCM1 group, respectively. Thirty-three out of 71 (46%) presented to the ED with some iron status parameters (serum ferritin, serum iron or transferrin), which were complete in 48% of the cases. In 14/71 (20%), iron status was tested in the ED. In the remaining 24, iron parameters were not available but patients had a documented history of IDA. In the analysis of (co)variance, older age, male sex, presence of symptoms, and lower Hb level at admission were found to be positively associated with rate of transfused patients. Differences between FCM0 and FCM1 groups were found to be non-significant relating to age, male sex and presence of symptoms, while a tendency towards lower Hb levels at ED admission in the FCM1 group emerged.

Table 1 Demographic and clinical characteristics at T0 (emergency department admission)

	FCM1 ($n=23$)	FCM0 ($n=48$)	*P* value
Sex F, *n* (%)	20 (87)	40 (83)	0.69
Age, years[a]	43 ± 8	41 ± 9	0.46
History of IDA, *n* (%)	15 (65)	31 (65)	0.96
Symptoms, *n* (%)	17 (74)	29 (60)	0.27
Syncope or pre-syncope, *n* (%)	3 (13)	5 (10)	0.71
Hematological parameters			
Hb, g/dL[a]	6.3 ± 0.9	6.7 ± 0.8	0.06
MCV, fL[a]	61 ± 8	62 ± 5	0.57
RDW, %[a]	20 ± 3	20 ± 2	0.70
RBC, 10^{12}/μL[a]	3.8 ± 0.5	3.9 ± 0.5	0.25
PLT, 10^{3}/μL[a]	340 ± 83	378 ± 105	0.12
Ferritin, mcg/L[a]	3 ± 2	5 ± 4	0.17
TSAT, %[a]	3 ± 1	4 ± 3	0.18

IDA iron deficiency anemia, *FCM1* patients treated with ferric carboxymaltose in the emergency department, *FCM0* patients not treated with ferric carboxymaltose in the emergency department, *Hb* hemoglobin, *MCV* mean cellular volume, *RDW* RBC distribution width, *RBC* red blood cells, *PLT* platelets, *Retics* reticulocytes, *pts* patients, *TSAT* transferrin saturation

[a]Results are expressed as mean ± SD

Treatment in the ED

In the FCM1 group, 13 patients received 500 mg of FCM and 10 received 1000 mg. No adverse events were observed.

Nineteen out of 48 (40%) in the FCM0 group were transfused (Table 2), 5 with 1 unit, 13 with 2 units and 1 with 3 units; 4 out of 19 were asymptomatic. In the FCM1 group, 3/23 (13%) were transfused (Table 2), 1 with 2 units and 2 with 1 unit; at the ED admission they all complained of symptoms related to anemia.

The lower transfusion risk (RR = 0.29, 95% CI 0.10–0.85) in the FCM1 group was confirmed in an adjusted robust Poisson analysis. Considering the 48 patients who were not treated with FCM, 19 presented to the ED after 2016, when FCM was already available in the ED.

At discharge from the ED (T1), Hb values were 7.5 ± 1.1 g/dL in the FCM0 and 6.5 ± 0.9 g/dL in the FCM1 group ($p=0.002$); this difference was due to the higher use of RBC transfusion in the FCM0 group.

Table 2 Treatment in the emergency department in the FCM0 and FCM1 group

	FCM1 ($n=23$)	FCM0 ($n=48$)	*p* value
Patients transfused, *n* (%)	3 (13)	19 (40)	0.02
Units per patient[a]	0.2 ± 0.5	0.7 ± 0.9	0.02
Units per transfused patient[a]	1.3 ± 0.6	1.8 ± 0.5	0.17
Patients hospitalized, *n* (%)	0 (0)	10 (21)	0.02

FCM1 group trated with ferric carboxymaltose, *FCM0* group not treated with ferric carboxymaltose

[a]Results are expressed as mean ± SD

All the patients in the FCM1 group were discharged, while 21% in the FCM0 were admitted to the ward (0/23 vs 10/48, $p=0.02$) (Table 2). Among those discharged in the FCM0 group, oral iron was prescribed in 29 patients, with variable dosage (30–315 mg per day in single or divided dose), while 9 did not receive any iron prescription. The lowest value of Hb at discharge was 4.7 g/dL, in the FCM1 group.

Efficacy and safety of FCM at short- and long-term follow-up.

Twenty patients in the FCM1 group presented to a short-term hematological evaluation in the hospital anemia clinic (T2, 11 ± 3 days after discharge). In the anemia clinic, patients who had received 500 mg in the ED, were treated with further 500 mg. The net Hb increase from T1 to T2 in the FCM1 group was 2.8 ± 1 g/dL and at T2 a high mean reticulocyte count was observed (162×10^3/mcl ± 86×10^3/mcl). Data from a comparable timepoint (9 ± 5 days) were available for 14 patients in the FCM0 group in which the net Hb increase from T1 to T2 was 0.8 ± 1 g/dL ($p<0.01$).

Sixteen FCM1 patients were followed for a long-term follow-up (T3) at 52 ± 28 days, median 42, range 27–122 days (Table 3): at T3, the mean Hb value was 11.8 ± 1.1 g/dL and the net Hb increase from T0 to T3 was 5.3 ± 1.4 g/dL.

Discussion

Our retrospective study showed significant variability in the management of hemodynamically stable patients presenting to the ED with severe IDA. This seems most likely due to the absence of specific guidelines. Thus, physicians' approach differs according to their experience and education. In our institution, ED staff with previous experience in hematological-anemia clinic was more prone to use IV iron and to discharge patients with extremely low Hb levels than other colleagues. The lowest Hb level at discharge was 4.7 g/dL in a 41-year-old man with chronic hemorrhoid bleeding; he was asymptomatic at rest, declined to receive 1 unit of RBCs and was treated with 1000 mg of FCM before being discharged.

In addition to this case, seven more patients were discharged with a Hb level below 6 g/dL and the mean Hb value in our cohort (6.3 ± 0.9 g/dL) was significantly lower compared to Quintana-Diaz et al.'s cohort (8.3 ± 1.4 g/dL) [21].

We focused on severe anemia because published guidelines for transfusion thresholds refer only to hospitalized patients, while no guidelines exist for out-patient management of anemia. Our decisions to transfuse, as well as to discharge or admit, are often based on unsubstantiated hemoglobin level and are further complicated by regulatory constraints and by fear of future litigation [22], while they should be based on a comprehensive evaluation of patient's history, clinical signs and symptoms.

All the patients treated with IV iron were discharged, whereas 21% of the FCM0 group were admitted to the ward, including two who declined to receive blood transfusion, both in the pre-FCM phase. This different attitude could be explained by the fact that a patient with severe IDA, who is not actively bleeding, if treated with FCM, can be discharged after the specific treatment, which makes the physician more confident that hemoglobin correction will occur.

This might have also influenced the choice to transfuse or not transfuse in the two groups, since in the group treated with FCM, we observed a significantly lower use of RBC transfusions compared to those not treated with FCM. Not only the rate of transfused subjects was lower (13 vs 40%), but we also observed a tendency towards fewer units per transfused patient, although not statistically significant.

Our data demonstrate the need to implement the AABB recommendations of the Choosing Wisely campaign: "Don't transfuse RBCs for iron deficiency without hemodynamic instability." [9]. Educational intervention has proven to increase appropriateness of RBC transfusions in the ED [10] setting, thus such programs should be broadly implemented underling the importance of alternative options, such as IV iron. In our study, treatment with FCM effectively and rapidly increased Hb level, producing a mean net Hb increase of 2.8 ± 1 g/dL in less than 2 weeks and an increase of 5.3 ± 1.4 g/dL in 52 ± 28 days.

No adverse events were reported. In this retrospective study, no data have been collected about hypophosphatemia, which is related to FCM infusion in approximately half of the cases [23]; however, no symptoms were complained. Nevertheless, data show that a single infusion is very unlikely to have a clinical significance [24].

Table 3 Hematological parameters at T0 (admission to the emergency department), at a short-term follow-up (T2, FCM1: 11 ± 3 days) and a long-term follow-up (T3, FCM1: 52 ± 28 days, median 42, range 27–122 days) among patients treated with FCM (ferric carboxymaltose)

	T0 ($n=23$)	T2 ($n=20$)	T3 ($n=16$)
Hb, g/dL[a]	6.3 ± 0.9	9.3 ± 1.1	11.8 ± 1.1
MCV, fL[a]	61 ± 8	72 ± 7	80 ± 7
RDW, %[a]	20 ± 3	28 ± 5	18 ± 6
RBC, $\times10^{12}$/μL[a]	3.8 ± 0.5	4.5 ± 0.4	4.6 ± 0.4
PLT, $\times10^3$/μL[a]	340 ± 83	311 ± 88	256 ± 90
Reticulocytes, $\times10^3$/μL[a]	–	162 ± 86	–
Hb change from ED discharge, g/dL[a]	–	2.8 ± 1	5.3 ± 1.4

Hb hemoglobin, *MCV* mean cellular volume, *RDW* RBC distribution width, *RBC* red blood cells, *PLT* platelets

[a]Results are expressed as mean ± SD

Among the 20 FCM1 patients who have been evaluated for a short-term follow-up (T2), none presented complications of severe anemia nor presented to another physician or emergency service after discharge. We can conclude that in patients with specific characteristics, especially hemodynamic stability and absence of active bleeding, the administration of IV iron has a good safety profile. Furthermore, administration of IV iron is fast and does not require tests for preparation as in the case of RBC transfusions.

From a hematological point of view, at T3 (52 ± 28 days), we observed a normalization of thrombocytosis and mean cellular volume (MCV) and a trend towards the normalization of RDW (RBC distribution width), that was significantly high at T2 (11 ± 3 days) because of the coexistence of two different erythroid populations (reticulocytes and microcytic red cells produced during the ID phase). Data at T2 from the FCM0 group, although with some limitations related to the number of subjects and their heterogeneity, including admitted and non-admitted patients, show a significantly lower increase of Hb that can be related either to the absence of a specific treatment (e.g., IV iron) or the suppression of EPO after transfusion [25].

In terms of appropriateness, we want to point out that among those who presented with iron status exams requested by the general practitioner, only 48% had a complete iron status (including serum ferritin, iron and transferrin). Again, this underlines the importance of physicians' education. In 14 patients, iron status was performed in the ED. These tests are often considered non-urgent and inappropriate for the ED setting. However, we believe that the availability of the iron status in some cases can drive physicians' decision in terms of diagnostic and therapeutic approach, offering a more appropriate strategy, as also suggested by Beverina et al. [11]

Although costs analysis was not the purpose of our study, considering the significant costs of RBC transfusion and the higher rate of hospital admission in the FCM0 group, administration of IV iron in the ED could be cost saving, as shown by Quintana-Diaz et al. [26].

Several limitations to this study need to be acknowledged. First of all being a retrospective study, inclusion and exclusion criteria were evaluated according to the ED report, thus we cannot exclude selection bias. We excluded patients with hemodynamic instability, history of cardiovascular disease, chest pain, EKG alterations and active bleeding, with the exception of menstrual bleeding. We also excluded pregnant women because in our institution they are evaluated in the Obstetric and Gynecologic ED with a separated follow-up.

We also excluded subjects older than 55 years of age, because we aimed to focus on a well-defined population to verify if extremely low levels of hemoglobin were safe and could be managed with IV iron and/or in an out-patient clinic, instead of hospitalization. In fact, an older population would have included more fragile patients with multimorbidity, who would require a dedicated study.

However, we believe that our preliminary data are promising and focus on an unmet need that requires a clinical trial with a higher number of patients to define Hb transfusion thresholds in the out-patient setting and to consolidate the use of high-dose IV iron in the ED.

In conclusion, administration of IV iron in the ED for severe chronic IDA in hemodynamically stable patients was associated with less need for transfusion, fewer hospital admissions compared to other treatment options and an extremely good efficacy and safety profile in this population. No adverse events were observed. Implementation of physicians' education is necessary and further studies are needed to develop recommendations for the management of IDA in the ED.

Author contributions Irene Motta, Giulia Mantovan, Dario Consonni, Nicola Montano and Maria Domenica Cappellini contributed to the study conception and design. Material preparation, data collection and analysis were performed by Giulia Mantovan, Irene Motta and Dario Consonni. Irene Motta, Anna Maria Brambilla, Maria Materia, Marianna Porzio and Margherita Migone De Amicis took care of patients. The first draft of the manuscript was written by Irene Motta and Giulia Mantovan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest IM received honoraria from Sanofi-Genzyme; NM received honoraria for lecturing from Novo Nordisk; MDC member of Vifor, Sanofi-Genzyme, Celgene, Novartis and Bluebird advisory Board**.**

Statement of human and animal rights This study was approved by the Institutional Ethics Committee of our institution.

Informed consent For this type of study informed consent is not required.

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