Brief report

A synchronized approach between emergency department and anemia clinic to intravenous iron treatment for very severe (Hb <7.0 g/dL) and extreme (<5.0 g/dL) iron-deficiency anemia: short-, medium- and long-term efficacy and safety analysis

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INTRODUCTION

Iron deficiency is the main cause of anemia worldwide, regardless of geographical area, income, age, or gender. It is estimated that about a sixth of the world's population is affected by iron-deficiency anemia (IDA), which therefore constitutes a global public health issue[1].

For patients admitted to Emergency Departments (ED), prompt and effective treatment of chronic IDA without a blood transfusion may result in a swift and stable hematopoietic and clinical recovery in many cases[2,3].

In this regard, experienced anemia clinics (AC) play a crucial role in the diagnosis, treatment, and follow-up of IDA on an outpatient basis, functioning both as the first treatment center and as the setting for follow-up of intravenous (IV) iron infusions administered in the ED.

The aim of the present study was to evaluate the short-, medium- and long-term results of our shared treatment path in patients with critical hemoglobin values.

MATERIALS AND METHODS

Patients and data collection

Baseline and follow-up data were collected for patients who had undergone IV iron infusion without transfusion for chronic very severe (hemoglobin [Hb] <7.0 g/dL) and extreme (Hb <5.0 g/dL) IDA admitted to the ED or evaluated at the AC from June 2019 to May 2022.

Baseline assessments evaluated the following hemato-chemical and physiological parameters: Hb concentration, hematocrit, mean corpuscular volume, platelet count, transferrin saturation, ferritin concentration, blood pressure, and heart rate. After a diagnosis of chronic IDA had been made, patients were treated with IV iron immediately. All patients were then sent home and monitored clinically by their general practitioner during the period prior to their next AC appointment.

At the second assessment (short-term evaluation), reticulocyte count was added to the blood cell count, and a further IV infusion was administered. At the third assessment (medium-term evaluation) all the hemato-chemical and physiological parameters were reassessed. Further investigations that were ordered, on a non-systematic basis, included oxygen saturation on admission and folate, vitamin B12, and phosphate concentrations during treatment.

At baseline and over the course of treatment, all patients were evaluated for the absence

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of risk factors indicating the necessity for prompt transfusion therapy. The following pre-existing conditions were classified as cardiovascular comorbidities: coronary artery disease, myocardial infarction, cerebrovascular accident, and peripheral artery disease.

All patients were tracked as regards the need for further iron infusions, transfusion therapy and readmissions to the ED from the third visit to the present (long-term evaluation).

Interventions

Ferric carboxymaltose (FCM; Ferinject®, Vifor Pharma, St. Gallen, Switzerland) was administered as described in the product data sheet. When below the lower limit of normal, folate deficiency was corrected using oral (Folina® 5 mg, Teofarma, Pavia, Italy) or IV therapy (Levofolene® 25 mg, Alfasigma, Milan, Italy) and vitamin B12 using oral supplements or intramuscular injections (Dobetin 1000®, Angelini Pharma, Rome, Italy). Oral supplements were prescribed in cases of phosphate deficiency.

The study was approved by the Hospital Blood Transfusion Committee, and since it involved the application in the ED of diagnostic and therapeutic best practices already in use in the AC, approval from the Ethics Committee was not considered necessary.

Statistical analysis

Data are shown as counts and percentages with their mean ± standard deviation (SD) or median ± interquartile range (IQR). The Pearson's chi-square test with Yates' correction or Fisher's exact test, when indicated, were performed to assess the differences between categorical variables. The two-tailed Student's t-test was used in the event of normally distributed continuous variables, whereas the Mann-Whitney or Kruskal-Wallis test was used for non-normally distributed continuous variables. To measure the strength of linear association between variables, the Pearson product-moment correlation coefficient (r) was used when indicated.

Data were analyzed using SPSS software (version 20, IBM, Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Table I - *Baseline data and days of follow-up*

	Overall n.=47	ED n.=28	AC n.=19	p
Gender, male/female	5/42	4/24	1/18	0.635
Age, years	58 (21)	50 (15)	71 (24)	**0.001**
≤50, n. (%)	22 (46.8)	16 (57.2)	6 (31.6)	0.136
> 50 ≥65, n. (%)	7 (14.9)	6 (21.4)	1 (5.3)	0.215
>65 ≥80, n. (%)	10 (21.3)	6 (21.4)	4 (21.0)	1.000
>80, n. (%)	8 (17.0)	0 (0.0)	8 (42.1)	**<0.001**
SBP (mmHg)	130 (17)	132 (18)	127 (14)	0.318
DBP (mmHg)	73 (9)	70 (9)	76 (6)	**0.022**
Heart rate (bpm)	85 (12)	87 (14)	81 (8)	0.112
Oxygen saturation (%)	99 (1)	99 (1)	98 (2)*	0.104
Diagnosis				
Gastrointestinal bleeding, n. (%)	23 (48.9)	13 (46.4)	10 (52.6)	1.000
Gynecological bleeding, n. (%)	21 (44.7)	13 (46.4)	8 (42.1)	0.770
Malabsorption, n. (%)	3 (6.4)	2 (7.2)	1 (5.3)	1.000
Hemoglobin (g/dL)	6.4 [5.5-6.7]	6.0 [5.3-6.7]	6.5 [6.3-6.8]	0.171
6.0-6.9, n. (%)	29 (61.7)	14 (50.0)	15 (78.9)	0.068
5.0-5.9, n. (%)	10 (21.3)	9 (32.1)	1 (5.3)	**0.034**
4.0-4.9, n. (%)	5 (10.6)	4 (14.3)	1 (5.3)	0.635
<4.0, n. (%)	3 (6.4)	1 (3.6)	2 (10.5)	0.557
Follow-up (days)	658 [444-751]	589 [383-766]	680 [514-749]	0.474
Patients transfused at follow-up	0 (0)	0 (0)	0 (0)	1.000

Data are shown as mean (± standard deviation) or median [interquartile range]. *Assessed in three patients with Hb <5.0 g/dL. ED: Emergency Department; AC: Anemia Clinic; SBP: systolic blood pressure; DBP: diastolic blood pressure.

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RESULTS

Over the study period, 47 patients with Hb <7.0 g/dL met the inclusion criteria. Blood transfusion was not an option for one of them. That patient completed the therapeutic cycle twice. The patients' baseline data are shown in **Table I**.

Vitamin B12, folate, and phosphate levels were assessed in 38, 32, and 17 patients respectively, and oral, intramuscular, or intravenous supplementation was given in 7.9%, 21.9%, and 70.6% of patients respectively.

The dosage of IV iron, the differences between the baseline laboratory values and those recorded at the second and third visits are shown in **Table II**. At a mean (±SD) of 10 (±3) and 35 (±12) days after the first infusion, the Hb concentration had increased by 2.3 g/dL (IQR: 1.8-3.1) and 5.8 g/dL (IQR: 4.9-6.4), respectively. **Figure 1A** shows the recovery of Hb concentration for all patients and by cause of the IDA.

The differences in Hb recovery between young/middle-aged (≤65 years) and older (>65 years) patients were not statistically significant (first visit-intermediate

Table II - *Comparisons between pre-, intermediate, and post-therapy parameters*

Parameter	Visits			p
	Baseline assessment	Second assessment	Third assessment	
FCM dose (g)	1.0 [1.0-1.0]	0.5 [0.5-1.0]	--	**<0.001**
Days from first infusion	--	10 (3)	35 (12)	--
Hemoglobin (g/dL)	6.4 [5.5-6.7]	8.5 [7.9-9.0]	11.7 [11.2-12.8]	**<0.001**
Δ Hb (g/dL)	--	2.3 [1.8–3.1]	5.8 [4.9–6.4]	--
MCV (fL)	61.7 [57.3-68.3]	73.2 [68.9-81.4]	83.1 [79.1-90.1]	**<0.001**
Reticulocytes (%)	n.a.	5.2 [3.9-8.6]	1.0 [0.6-1.5]	**<0.001**
Platelets (x 10^3/µL)	332 (111)	282 (105)	245 (77)	**<0.001**
TSat (%)	3 [2-4]	n.a.	21 [15-25]	**<0.001**
Ferritin (ng/mL)	4 [2-8]	n.a.	161 [80-335]	**<0.001**

Data are shown as mean (± standard deviation) or median [interquartile range]. FCM: ferric carboxymaltose; Δ Hb: change in hemoglobin concentration; MCV: mean corpuscular volume; TSat: transferrin saturation; n.a.: not assessed. Except for the reticulocyte count, statistical analyses were performed between baseline values and final values.

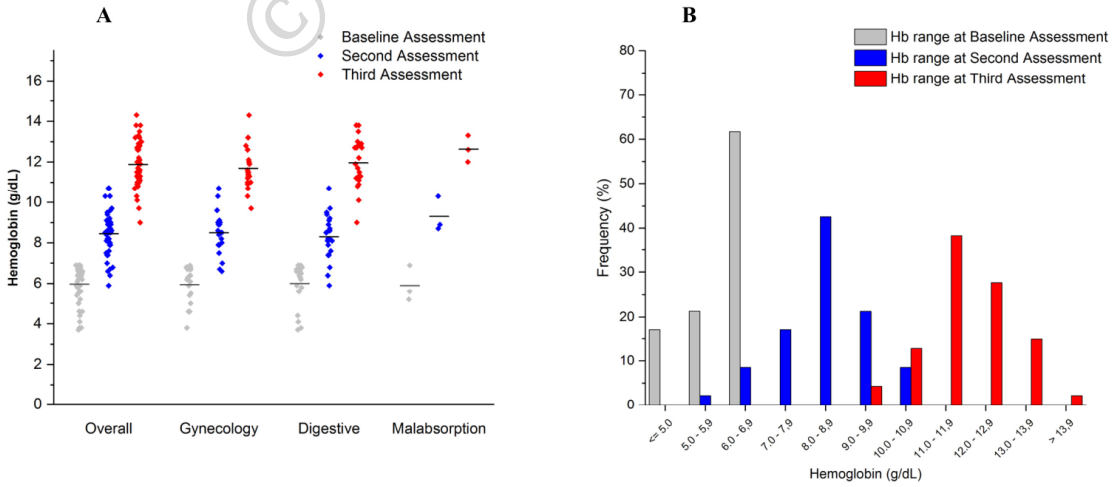

Figure 1 - Hemoglobin recovery (A) and changes in hemoglobin range (B) from the baseline to the first and second assessments

visit, p=0.529; first visit-final visit, p=0.083), whereas a statistically significant inverse correlation was seen between baseline and Hb recovery (p<0.001).

At an average of 10 days after the first infusion, 33 patients (70.2%) had reached Hb values of more than 8.0 g/dL. The three patients with a Hb of 3.7, 3.8, and 3.8 g/dL at the second assessment reached Hb levels of 6.8, 7.4, and 7.5 g/dL, respectively.

As shown in **Figure 1B**, at the third assessment, 45 patients (95.7 %) had a Hb of more than 10.0 g/dL. The range of total Hb improvement was between 5.0 g/dL and 6.0 g/dL in 34 patients (72.3%). No patients experienced side effects.

At an average follow-up of 616 days (range, 60-1,131), no patients had been transfused or readmitted to the ED. After the third assessment, 20 (42.6%) received further infusions (median 2, IQR 1-4, minimum 1-maximum 7) in the AC.

One 95-year-old patient died 2 months after the last dose of IV iron due to colorectal cancer.

DISCUSSION

The ED is often the first point of access for patients with previously known anemia and occasionally for those diagnosed with anemia as a result of laboratory tests prescribed for other reasons. Blood transfusion is a frequent therapeutic approach in the emergency setting[4]. However, as demonstrated over several decades, it can induce a series of well-known side effects, including transfusion-associated cardiac overload, transfusion-related acute lung injury, and immunosuppression, to name a few[5]. A further significant cause for concern regarding the transfusion of blood is the increasing shortage of this essential resource due to the predicted progressive aging of the population[6]. Thus, closer adherence to guidelines and the application of the three pillars of the Patient Blood Management (PBM) methodology should be encouraged in order to improve patients' health and conserve resources[7,8].

In this respect, second- and third-generation IV iron products have proven to be an effective and safe alternative to blood transfusion in most cases of severe IDA[9] and should be the first-choice therapy in hemodynamically stable patients[10,11]. Unfortunately, the use of these products continues to be limited as a result of several misconceptions[9].

Legnano General Hospital is a 530-bed tertiary care hospital located in northern Italy with a catchment area of more than 470,000 people. The mean number of patients who access the ED is approximately 60,000 per year. In 2018 the ED and AC in our hospital adopted a synchronized approach to the treatment of patients with severe IDA with the objective of offering the most appropriate treatment, as swiftly as possible, at the first point of admission and subsequently proceeding with additional therapy and follow-up. During the period under review, 427 patients were treated with IV iron. During the same time frame, 2,353 iron infusions were administered in the AC. Despite the high prevalence of anemia in the ED[12], few studies have focused on transfusion practices in this clinical setting and all have shown a high level of inappropriate transfusions along with an underuse of intravenous iron therapy in patients affected by IDA[3,12-18].

A previous study conducted by our group demonstrated that the implementation of a PBM protocol in the ED was effective in reducing the number of inappropriate transfusions, hospital admissions, time spent in hospital, and costs[2]. In a joint Spanish-Italian study, a subset of 87 patients admitted to the ED with IDA and Hb <7.0 g/dL were safely and effectively treated in the AC with IV iron therapy only[3].

In the present study, all patients were hemodynamically stable, with no likelihood of impending blood loss; this is a prerequisite for choosing a restrictive approach to the administration of transfusions. To our knowledge, this is the first study to evaluate the short-term efficacy of IV iron in patients with very low Hb levels. As already proven[14,3], there is an inverse correlation between baseline Hb and the extent of Hb global recovery. The same correlation was seen at the first assessment after a median of 10 days in our series (p=0.027). The three patients with extreme anemia experienced a fast Hb recovery with safe values of approximately 7.0 g/dL at the first assessment. This is in line with the evidence of a prompt reticulocyte crisis that starts a few hours after IV iron therapy[19] and emphasizes the importance of a global assessment of patients despite their Hb value.

None of the patients were transfused or readmitted to the ED during the follow-up, as evidence of complete hematopoietic recovery and restored health. Twenty patients (40.6%) achieved complete recovery following additional iron infusions, with no side effects. These data highlight the need for regular monitoring of Hb and iron in the months following correction of IDA.

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Notably, slightly more than two-thirds of patients evaluated for this aspect developed hypophosphatemia, a frequent side effect of ferric carboxymaltose therapy[20], which requires oral supplementation. However, none of them had any clinical consequences from the phosphate deficiency. Moreover, pre-infusion values were not recorded, making it impossible to exclude a pre-existing condition.

The study has several limitations in addition to the low number of patients. The retrospective design should be considered a limitation *per se*. However, conducting a randomized, prospective study at Legnano General Hospital would raise ethical issues given the evidence of the efficacy and safety of our approach that has already been gathered over time. Furthermore, the data collected are only for patients referred from the ED to the AC; it is, therefore, possible that subjects who would have met the enrolment criteria were not included. Lastly, it is not known whether patients were transfused at other hospitals during the follow-up, which may have caused an underestimation of the number of patients transfused throughout the study period. However, since all patients resided in the vicinity of the place of treatment, this is unlikely.

CONCLUSIONS

Albeit in a limited number of cases, our study confirms the feasibility, efficacy, and safety of transfusion-free management of very severe and extreme IDA. In order to promote patients' safety and better use of resources, we feel that a PBM-based, synchronized approach between the ED and the AC should be standard practice.

AUTHORSHIP CONTRIBUTIONS

IB designed the study, collected, analyzed and interpreted data, wrote the manuscript, and treated patients in the anemia clinic. MR wrote the manuscript and treated patients in the Emergency Department.

Keywords: anemia clinic, Emergency Department, intravenous iron, patient blood management.

DISCLOSURE OF CONFLICTS OF INTEREST

IB has received financial support for travel expenses and conference registration from Vifor Pharma. MR has no conflicts of interest to disclose.

REFERENCES

1. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014; 123: 615-624. doi: 10.1182/blood-2013-06-508325.
2. Beverina I, Razionale G, Ranzini M, Aloni A, Finazzi S, Brando B. Early intravenous iron administration in the Emergency Department reduces red blood cell unit transfusion, hospitalisation, re-transfusion, length of stay and costs. Blood Transfus 2020; 18:106-116. doi: 10.2450/2019.0248-19.
3. Jericó C, Beverina I, Quintana-Diaz M, Salvadori U, Melli C, Rondinelli MB, et al. Efficacy and safety of high-dose intravenous iron as the first-choice therapy in outpatients with severe iron deficiency anemia. Transfusion 2020; 60: 1443-1449. doi: 10.1111/trf.15870.
4. Facco G, Bennardello F, Fiorin F, Galassi C, Monagheddu C, Berti P, et al. A nationwide survey of clinical use of blood in Italy. Blood Transfus 2021;19: 384-395. doi:10.2450/2021.0083-21.
5. Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. N Engl J Med 2017; 377: 1261-1272. doi: 10.1056/NEJMra1612789.
6. Farmer SL, Towler SC, Leahy MF, Hofmann A. Drivers for change: Western Australia Patient Blood Management Program (WA PBMP), World Health Assembly (WHA) and Advisory Committee on Blood Safety and Availability (ACBSA). Best Pract Res Clin Anaesthesiol 2013; 27: 43-58. doi: 10.1016/j.bpa.2012.12.007.
7. Hofmann A, Shander A, Blumberg N, Hamdorf JM, Isbister JP, Gross I. Patient blood management: improving outcomes for millions while saving billions. What is holding it up? Anesth Analg 2022; 135:511-523. doi: 10.1213/ANE.0000000000006138.
8. Spahn DR, Muñoz M, Klein AA, Levy JH, Zacharowski K. Patient blood management. Anesthesiology 2020; 133: 212-222. doi: 10.1097/ALN.0000000000003198.
9. Muñoz M, Gómez-Ramírez S, Besser M, Pavía J, Gomollón F, Liumbruno GM, et al. Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus 2017; 15: 422-437 doi: 10.2450/2017.0113-17.
10. Shander A, Muñoz M, Spahn DR. Intravenous iron for severe iron deficiency anaemia. Br J Anaesth 2018; 121:342-344. doi: 10.1016/j.bja.2018.05.055.
11. Callum JL, Waters JH, Shaz BH, Sloan SR, Murphy MF. The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. Transfusion 2014; 54: 2344-2352. doi: 10.1111/trf.12802
12. Beverina I, Brando B. Prevalence of anemia and therapeutic behavior in the emergency department at a tertiary care hospital: are patient blood management principles applied? Transfus Apher Sci 2019; 58:688-692. doi: 10.1016/j.transci.2019.07.006.
13. Spradbrow J, Lin Y, Shelton D, Callum J. Iron deficiency anemia in the emergency department: over-utilization of red blood cell transfusion and infrequent use of iron supplementation. CJEM 2017; 19:167-174. doi: 10.1017/cem.2016.388.
14. Quintana-Díaz M, Fabra-Cadenas S, Gómez-Ramírez S, Martínez-Virto A, García-Erce JA, Muñoz M. A fast-track anaemia clinic in the emergency department: feasibility and efficacy of intravenous iron administration for treating sub-acute iron deficiency anaemia. Blood Transfus 2016; 14:126-133. doi: 10.2450/2015.0176-15.
15. Quintana-Díaz M, Borobia AM, García Erce JA, Maroun-Eid C, Fabra S, Carcas A, et al., USEES-URG Research Group. Appropriate use of red blood cell transfusion in emergency departments: a study in five emergency departments. Blood Transfus 2017; 15:199-206. doi: 10.2450/2016.0324-15.
16. Khadadah F, Callum J, Shelton D, Lin Y. Improving quality of care for patients with iron deficiency anemia presenting to the emergency department. Transfusion 2018; 58:1902-1908. doi: 10.1111/trf.14626.
17. Motta I, Mantovan G, Consonni D, Brambilla AM, Materia M, Porzio M, et al. Treatment with ferric carboxymaltose in stable patients with severe iron deficiency anemia in the emergency department. Intern Emerg Med 2019; 15:629-634. doi: 10.1007/s11739-019-02223-z>.
18. Boone S, Peacock WF, Ordonez E, Powers JM. Management of nonpregnant women presenting to the emergency department with iron deficiency anemia caused by uterine blood loss: a retrospective cohort study. J Emerg Med 2020; 59: 348-356. doi: 10.1016/j.jemermed.2020.05.006.
19. Ding Y, Zhu X, Li X, Zhang H, Wu M, Liu J, et al. Pharmacokinetic, pharmacodynamic, and safety profiles of ferric carboxymaltose in Chinese patients with iron-deficiency anemia. Clin Ther 2020; 42:276-285. doi: 10.1016/j.clinthera.2019.12.010.
20. Schaefer B, Tobiasch M, Wagner S, Glodny B, Tilg H, Wolf M, Zoller H. Hypophosphatemia after intravenous iron therapy: Comprehensive review of clinical findings and recommendations for management. Bone 2022; 154:116202. doi: 10.1016/j.bone.2021.116202.