Clinical experience with ferric carboxymaltose in the management of anemia in acute gastrointestinal bleeding

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Introduction

Acute gastrointestinal bleeding (AGIB) is a common cause of hospitalization. Recent prospective studies have estimated the incidence to be 87 cases per 100,000 population for acute upper or lower gastrointestinal (GI) bleeding [1,2], and up to 76 patients are hospitalized per 100,000 population as a result [3,4]. Mortality is high, with estimates typically in the range 3–14% [5–7].

The immediate clinical priority is to stabilize the patient, stop the hemorrhage, and where necessary use blood transfusion to correct severe anemia [8]. Blood transfusion is widely used in cases of AGIB, but it is increasingly being recognized that overtransfusion should be avoided to improve survival rates [9]. Transfusion increases the risk of nosocomial infection and is associated with increased mortality in high-risk hospitalized patients [10], as well as incurring substantial financial costs. Moreover, it is associated with an increased risk for rebleeding and higher mortality [9,11]. Restricted use of blood transfusion, whereby it is administered only to patients with very low hemoglobin (Hb) levels, has become the standard of care in many types of AGIB [12]. European and US guidelines recommend a restrictive transfusion strategy that targets a Hb level between 7 and 9 g/dl or higher Hb target levels if the patient has intravascular volume depletion or significant comorbidity such as ischemic cardiovascular disease [13,14]. A recent meta-analysis of five randomized-controlled trials showed that compared with a liberal transfusion strategy, restrictive transfusion is associated with a significant reduction in all-cause mortality [15].

Longer-term restoration of normal Hb levels after AGIB, however, is often neglected. Current recommendations do not address the use of iron supplementation [13,14] despite the fact that anemia affects 50–80% of patients discharged after AGIB [16–18] and iron deficiency has been documented in ~50% of patients at discharge [19]. Management of anemia is clearly important in this
population, but a survey conducted in Canada in 2016 found that fewer than 15% of clinicians prescribe iron therapy in patients who are anemic after AGIB, and that oral iron is the selected mode of administration in 80% of treated patients [20]. Another survey, in Denmark, reported that only 13% of discharged anemic patients are administered oral iron supplementation after AGIB, with none administered intravenous (i.v.) iron [16,21].

Some experts suggest that high-dose i.v. iron formulations would be logical after AGIB because iron replenishment is rapid and treatment is well tolerated, and i.v. therapy avoids the risk of poor compliance that can occur with oral iron treatment [22]. In recent years, new i.v. iron preparations have been developed that allow larger doses of iron to be administered in a single dose, reducing the cumulative risk for infusion reactions as well as improving convenience for physicians and patients [23]. One of these is ferric carboxymaltose (FCM), an i.v. iron preparation in which a nondextran, stable carbohydrate shell facilitates the release of iron in a controlled manner [24]. FCM can be infused in a single dose of up to 1000 mg iron over 15 min. A network meta-analysis of six randomized-controlled trials across various indications of chronic kidney disease [25], inflammatory bowel disease [26], postpartum anemia [27,28], heavy uterine bleeding [29], and fatigue [30] has shown that FCM improves levels of serum ferritin and transferrin saturation, and corrects Hb and fatigue [30] has shown that FCM improves levels of serum ferritin and transferrin saturation, and corrects Hb and fatigue. FCM was administered as a single dose of 1000 mg iron over 15 min during hospitalization after the patient had been stabilized. A follow-up visit took place ~2 months after discharge, and included blood sampling for the determination of Hb level [32].

The following information was obtained from patients’ medical records: demographic and clinical data, presentation and severity of AGIB (symptoms, hemodynamic instability, Charlson comorbidity index [33], Glasgow–Blatchford index score [34]), endoscopic features (cause of hemorrhage, endoscopic treatment, and Rockall index score [32]), medical treatment (number of blood transfusion units, total dose of FCM), Hb level (at hospital admission, the lowest value during hospital stay, at discharge, and at follow-up), and the duration of hospital stay. The mean change in Hb from the lowest value during hospitalization to (a) the value at hospital discharge and (b) the follow-up visit was calculated. Changes in Hb to both timepoints were also analyzed in the following subgroups: (i) patients aged younger than 75 or older than or equal to 75 years at admission (ii) patients with a Charlson comorbidity index less than 3 or at least 3 and (iii) patients with Hb above 10 g/dl or up to 10 g/dl at admission to hospital. These subgroups were considered to be high-risk populations: older age is associated with a higher risk of mortality; comorbidity as measured by the Charlson comorbidity index incurs a higher risk of mortality; and the Hb level indicates the severity of the GI bleeding (Hb ≤10 g/dl at hospital admission predicts iron deficiency anemia at 30 days after AGIB [18]).

Values are reported as \(n(\%)\) for categorical variables and as mean±SD values for continuous variables. Values were compared between subpopulations using the \(\chi^2\)-test, Student’s \(t\)-test, or paired \(t\)-test, as appropriate.

**Study conduct**

The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was approved by the Hospital Ethics Committee and Health Authorities (protocol number: RBC-HE-2018-01). All authors approved the procedures for data analysis and approved the final version of the manuscript for publication.

**Results**

**Study population**

In total, 84 patients were admitted with AGIB and treated with FCM during the study period. Seventy-nine (94.0%) patients had upper GI bleeding and five patients had lower GI bleeding (6%). The majority of patients (58/84) were male. The population had a high rate of comorbidities, with 51 (60.7%) patients having a Charlson comorbidity index score of at least 3. Thirteen (15.5%) patients had experienced previous AGIB (Table 1). Overall, only four patients had previously received antiaGGreGant medication, and Hb levels at admission, discharge, and follow-up in these individuals were similar to the rest of the study population. No other patient had been treated with antiaGGreGant therapy or nonsteroidal anti-inflammatory drugs. Two patients were admitted twice for AGIB bleeding and received FCM and blood transfusion on both occasions, such that a total of 86 episodes were analyzed.
Table 1. Demographic and clinical characteristics of patients admitted for acute gastrointestinal bleeding and treated with ferric carboxymaltose

| Characteristic                        | All patients (N = 84) | Transfusion + FCM (N = 88) | FCM (N = 26) |
|--------------------------------------|-----------------------|-----------------------------|--------------|
| **Sex (n [%])**                      |                       |                             |              |
| Male                                 | 58 (69.0)             | 39 (44.2)                   | 19 (73.1)    |
| Female                               | 26 (31.0)             | 20 (23.8)                   | 7 (26.9)     |
| **Age (years)**                      | 68.0 ± 16.9           | 70.0 ± 16.8                 | 63.2 ± 16.5  |
| (mean ± SD)                          |                       |                             |              |
| Charlon index [n (%)]                | 0                     | 2 (2.3)                     | 7 (28.6)     |
| Score 0                              | 5 (6.0)               | 2 (2.3)                     | 3 (11.5)     |
| Score 1–2                            | 20 (23.8)             | 13 (14.8)                   | 7 (27.0)     |
| Score 3–4                            | 27 (32.5)             | 17 (19.3)                   | 10 (38.5)    |
| Score ≥5                             | 24 (28.6)             | 21 (24.1)                   | 3 (11.5)     |
| Previous acute bleeding [n (%)]      | 13 (15.5)             | 7 (8.0)                     | 3 (11.5)     |

FCM, ferric carboxymaltose; Hb, hemoglobin.

*Two of these 84 patients were admitted twice. Among patients with Charlon index score ≥ 3; Hb data were missing in three patients (two transfusion + FCM, one FCM).

No statistically signiﬁcant differences. 

\(t\)-Test.

\(\chi^2\)-Test.

On admission, the majority presented with melanas [66/86 (76.7%)] and 21 (25.3%) patients presented with hematemesis. Approximately one in five [19/86 (22.1%)] had hemodynamic instability confirmed at hospital admission. Multiple presentations were common, with 17 patients having melena and symptoms of hemodynamic instability and nine having melena and hematemesis. In six (7%) patients, the initial symptom was weakness, presenting GI bleeding at admission. The most common causes of hemorrhage were duodenal and gastric ulceration (Table 2).

The mean ± SD levels of mean corpuscular hemoglobin (29.8 ± 3.38 pg) and mean corpuscular volume (90.1 ± 7.59 fl) across the study population were within the normal range at admission.

**Treatment and hospital stay**

The total dose of FCM was 1000 mg iron in 84/86 (96.5%) episodes, administered as a single infusion. In two further patients, who weighed less than 50 kg, a total dose of only 500 mg iron was calculated to be necessary. One patient was administered a dose of 1000 mg iron and also received an additional FCM dose of 500 mg iron after a low Hb value was recorded at the follow-up visit.

One or more blood transfusion was administered for 60/86 (69.8%) episodes using a mean of 3.0 ± 1.7 units of blood (Table 2). No oral iron or vitamin supplements were administered to any patient.

The mean hospital stay associated with AGIB was 7.9 ± 5.0 days. Patients requiring transfusion remained in hospital a mean of 8.2 ± 5.2 days compared with 7.2 ± 4.6 for those without transfusion (\(P < 0.0001\)).

The postdischarge follow-up visit at the hospital outpatient clinic took place at a mean of 60.9 ± 39.6 days after leaving hospital.

**Safety events**

There were no severe adverse events associated with FCM administration in any patient during hospitalization, and none were reported at the follow-up visit.

Table 2. Characteristics of acute gastrointestinal bleeding episodes in patients treated with ferric carboxymaltose

| Characteristic                        | All episodes (N = 86) | Transfusion + FCM (N = 88) | FCM (N = 26) |
|--------------------------------------|-----------------------|-----------------------------|--------------|
| **Clinical presentation [n [%]]**    |                       |                             |              |
| Hematemesis                          | 21 (23.5)             | 19 (21.3)                   | 14 (53.8)    |
| Melena                               | 66 (76.7)             | 50 (57.3)                   | 16 (61.5)    |
| Symptoms of hemodynamic instability  |                       |                             |              |
| Hemodynamic instability confirmed on admission [n [%]] | 19 (22.1) | 15 (20.5) | 4 (15.4) |

| Transfusion                           |                       |                             |              |
| Transformation                        | 47 (54.7)             | 40 (46.1)                   | 7 (26.9)     |

| Lowest in-hospital Hb (g/dl)          |                       |                             |              |
| Mean ± SD                            | 7.6 ± 0.8             | 7.2 ± 0.3                   | 8.8 ± 0.8    |

| GI bleeding                           |                       |                             |              |
| Mean ± SD                            | 81 (94.2)             | 57 (95.0)                   | 24 (92.3)    |

| Hospital admission [n [%]]            |                       |                             |              |
| Glasgow–Blatchford index (mean ± SD)  | 10.9 ± 2.7            | 11.8 ± 2.4                  | 8.8 ± 2.3    |

| Rockall index                         | 4.2 ± 1.7             | 4.5 ± 1.8                   | 3.5 ± 1.2    |

On discharge because of complications related to GI bleeding in a patient with multiple comorbidities.

| AGIB, acute gastrointestinal bleeding; FCM, ferric carboxymaltose; GI, gastrointestinal; Hb, hemoglobin.
| Including two patients who were admitted twice for two different AGIB episodes.

| Complications possible: melena + symptoms of hemodynamic instability 17, hematemesis + symptoms of hemodynamic instability 1; hematemesis + melena 9, melena + symptoms of hemodynamic instability + hematemesis 1.
| Syncope and/or dizziness.

| Defined as systolic blood pressure <100 mmHg with/without tachycardia, and signs of tissue hypoperfusion.

| Student’s t-test.

| One patient in the FCM group received an additional 500 mg iron dose after the follow-up visit.

One patient experienced a rebleeding episode in the upper GI tract because of cancerous ulcers at 3.5 months after hospital discharge. Two patients died because of underlying pathologies; one death occurred at 1 month after hospital discharge as a result of previously diagnosed pancreatic neoplasia and one death occurred 3 months after discharge because of complications related to GI bleeding in a patient with multiple comorbidities.

**Hemoglobin response**

In the total study cohort, the mean Hb at the time of hospital admission was 9.0 ± 2.2 g/dl, decreasing to 7.6 ± 1.3 g/dl at...
the lowest point during the hospital stay and before transfusion or administration of FCM. By the time of discharge, the mean Hb had increased to 9.4±1.1 g/dl (P < 0.001 vs. the lowest in-hospital Hb value). The increase in the mean Hb during the hospital stay was largely accounted for by the group who received one or more blood transfusion (Fig. 1). The lowest mean Hb level during hospitalization was lower in the group administered blood transfusion plus FCM versus FCM alone (7.2±1.3 vs. 8.8±0.6 g/dl, P < 0.001).

By the time of discharge, both groups had a similar mean Hb level (9.4±1.2 and 9.3±0.8 g/dl, respectively) (Fig. 1). At the postdischarge follow-up visit, the mean Hb was 12.7±2.4 g/dl (P < 0.001 vs. Hb at admission and vs. the lowest in-hospital Hb value).

The mean Hb was in the normal range both in the patients administered transfusion and FCM (12.4±2.5 g/dl) or FCM alone (13.7±1.8 g/dl) (Fig. 1). The Hb level was up to 10 g/dl at follow-up in 5/40 patients administered FCM plus transfusion FCM (13.9%) compared with 0/7 patients administered FCM alone. The increase in Hb from admission and from the lowest in-hospital Hb level to follow-up was significant with FCM with or without transfusion (P < 0.001 in all cases) (Fig. 1). At follow-up, Hb levels normalized (Hb ≥ 12 g/dl in women and ≥ 13 g/dl in men) in 60.0% of patients administered FCM plus transfusion versus 75.0% given FCM alone.

**Hemoglobin response in at-risk patient subpopulations**

Patients older than or equal to 75 years who received FCM plus transfusion [28/33 (84.8%)] had a mean Hb at admission of 8.0 versus 11.1 g/dl for those administered FCM alone (P = 0.001); Hb was 9.7 vs. 9.6 g/dl at discharge (NS) and 12.7 vs. 12.6 g/dl at follow-up (NS). Patients treated with FCM and transfusion who had a Charlson comorbidity index of at least 3 [36/46 (78.3%)] among patients for whom Hb data were available] had a mean Hb at admission of 7.9 versus 11.2 g/dl for FCM plus transfusion versus FCM alone (P < 0.001); the mean Hb was 9.6 versus 9.7 g/dl at discharge (NS) and 12.0 versus 13.1 g/dl at follow-up (NS). Finally, for patients with Hb of up to 10 g/dl at admission, the mean Hb at admission in the group administered FCM plus transfusion [40/47 (85.1%)] was 7.3 versus 9.1 g/dl in the FCM group (P = 0.004), 9.5 versus 8.9 g/dl at discharge (NS), and 12.6 versus 13.3 g/dl at follow-up (NS).

The mean increase in Hb from the lowest in-hospital Hb value to the point of discharge and to the follow-up visit was analyzed overall (Fig. 2a), in older patients (≥ 75 years (n = 33)) (Fig. 2b), in patients with the highest morbidity scores [Charlson index ≥ 3 (n = 48)] (Fig. 2c), and in patients with moderate or severe anemia [Hb ≤ 10 g/dl (n = 47)] at admission (Fig. 2d). These subgroups each showed a larger mean increase in Hb from the lowest in-hospital Hb value to the value at discharge than in their lower-risk counterparts: 2.1±1.7 versus 1.4±1.5 g/dl for patients aged older than or equal to 75 years versus younger than 75 years (P < 0.001); 1.9±1.6 versus 1.3±1.5 g/dl for patients with Charlson index of at least 3 versus less than 3 (P < 0.001); and 2.0±1.7 versus 1.0±1.3 g/dl for patients with Hb of up to 10 g/dl at admission versus more than 10 g/dl (P < 0.001).

In each of these subpopulations, the change in the mean Hb level to the follow-up visit was higher in the patients administered blood transfusion in addition to FCM versus FCM alone (Fig. 2b–d). However, even in patients administered only FCM, the mean Hb level was within the normal range or close to normal by the follow-up visit: 12.6±2.3 g/dl in patients aged older than or equal to 75 years, 13.1±2.0 g/dl in patients with Charlson index of at least 3, and 13.3±1.3 g/dl in patients with Hb of up to 10 g/dl at admission.

**Discussion**

International recommendations advise that transfusion should be restricted to cases of severe anemia (<7 g/dl) in patients with AGIB, except under specific circumstances [13,14]. At our center, use of blood transfusion was restricted to patients with the lowest Hb levels (mean...
7.2 g/dl at the lowest in-hospital measurement in the current cohort), a strategy shown to improve survival rates [9].

The rapid rate of erythropoiesis that is required after acute blood loss demands an adequate supply of iron. Well-designed trials of i.v. iron therapy in this setting are rare. A randomized comparative trial by Ferrer-Barceló et al. [35], which compared FCM versus oral iron in 55 patients with anemia after AGIB, showed a faster Hb response and normalization of transferrin saturation by day 7 with FCM versus oral iron, with fewer adverse events and improved tolerance in the FCM cohort. A double-blind, placebo-controlled study has been carried out in which 97 patients with nonvariceal upper GI hemorrhage were randomized to i.v. FCM, oral iron, or placebo [36]. The erythropoietic response was similar with either FCM or oral iron, but ferritin levels increased more rapidly with FCM (mean: 874 vs 149 μg/l at week 4). In our study, a single FCM dose was adequate to manage anemia without blood transfusion in 30% of patients. The mean Hb level at follow-up was either normal or close to normal both in patients administered transfusion and FCM and in those managed with FCM alone, with 60% of transfused patients and 75% of those receiving only FCM achieving normal Hb levels.

Three patient subpopulations considered to be at risk for poor outcomes were examined separately. The first group included older patients (≥75 years). Older age is a known risk factor for anemia, often associated with iron deficiency or renal insufficiency [37], and has been reported to increase the risk of anemia after AGIB [18]. Older patients may also be more likely to experience rebleeding and in-hospital mortality than younger patients [6,38,39]. The second group included patients with multiple comorbidities (Charlson comorbidity index ≥3). Highly comorbid patients frequently have primary or secondary renal dysfunction, reducing erythropoietin production and restricting erythropoiesis, with an associated increase in predicted health costs [40] and are at greater risk for death following AGIB [41]. The last group was patients with moderate or severe anemia at admission (≤10 g/dl). Low Hb (≤10 g/dl) at baseline is, as one would expect, predictive of subsequent anemia [18]. Hb less than 10 g/dl has been shown to be an independent predictor for rebleeding, need for intervention, or death following AGIB [42]. In these three groups, FCM alone achieved a mean Hb increase in the range 3.0–4.6 g/dl, and the mean Hb at follow-up was normal or close to normal.

According to our results, 15% of patients older than or equal to 75 years, 25% of patients with Charlson comorbidity index of at least 3, and 15% of patients with Hb of up to 10 g/dl at admission were managed only with FCM, achieving a significant increase in Hb and normalizing or almost normalizing Hb values at follow-up with a mean Hb of 12.6 g/dl in older than or equal to 75 years; 13.1 g/dl in Charlson index of at least 3; and 13.2 g/dl in those with Hb of up to 10 g/dl on admission.

These are encouraging findings, given the importance of achieving a sustained hematopoietic response and avoiding transfusion in these vulnerable patient groups.
In our series of 84 patients (86 AGIB episodes), no clinical adverse events were observed following FCM treatment. A meta-analysis of 11 randomized trials and three cohort studies of FCM at a dose of up to 1000 mg iron, in a range of clinical settings, has concluded that FCM is associated with fewer GI adverse events compared with oral iron, and that there are no FCM-related safety concerns [43]. Another recent meta-analysis, which compared different i.v. iron preparations, observed that FCM tends to be better tolerated than iron sucrose or iron isomaltoside [44].

This analysis reflects routine clinical practice, including the typical range of patients who present with AGIB. The only exclusion was patients with bleeding secondary to portal hypertension, which represents a different condition and requires different management. The major limitation of the study is the absence of a control group receiving only transfusions. In this group of patients with a high rate of comorbidities and low baseline Hb, routine practice at our center mandates i.v. iron to ensure rapid repletion of iron stores after acute hemorrhage. Second, as a retrospective analysis, transfusion decisions were made by the responsible clinician on the basis of the center’s standard restrictive transfusion policy. Third, data on Hb levels after hospital discharge were obtained at routine outpatient follow-up visits and the timing varied between patients. However, as production of new red cells takes ~25 days [45] and the mean interval between hospital discharge and the follow-up visit was 60 days, follow-up data are likely to have reflected the peak erythropoietic response to iron repletion by FCM. Finally, markers of iron status were only available infrequently in the patient records, reflecting the retrospective nature of the study. Thus, although the high rate of Hb normalization points to effective iron replenishment, this cannot be confirmed directly. However, the randomized study by Ferrer-Barceló et al. [35], which compared FCM versus oral iron in AGIB patients, reported significantly greater repletion of iron deposits under FCM versus oral iron at the end of the 6-week study (75 vs. 26% P = 0.0007).

Conclusion

Treatment with a single dose of FCM in patients with AGIB as part of a restrictive transfusion policy is associated with a good erythropoietic response and recovery from anemia after the immediate period of hospitalization. Although it is not the recommended dose to replenish iron deposits, a good erythropoietic response to a single infusion of FCM 1000 mg was observed in at-risk subgroups including patients aged older than or equal to 75 years, those with high comorbidity, and patients with moderate to severe anemia. Almost normal mean Hb values were achieved in these three groups, in whom improving Hb levels may be particularly important. FCM therapy was safe and well tolerated in this population, which included a high proportion of elderly patients and patients with multiple comorbidities, with no severe adverse events. Providing effective iron repletion during hospitalization through i.v. FCM therapy can help to avoid transfusion even in high-risk patients and also avoid the longer-term anemia so frequently observed after AGIB.

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Conflicts of interest

Mercedes Cucula-Ramos is an employee of Vifor Pharma España S.L. For the remaining authors, there are no conflicts of interest.

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