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Short-term treatment of iron deficiency anemia after cardiac surgery

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ABSTRACT

Iron deficiency anemia (IDA) is frequent after cardiac surgery and is associated with increased morbidity and mortality. In a retrospective study, we analyzed 106 patients with IDA (hemoglobin [Hb] $\leq$ 12 g/dl in women and $\leq$ 13 g/dl in men, transferrin saturation [TSAT] $\leq$ 20%) on admission to a Cardiac Rehabilitation Unit after cardiac surgery. The patients were divided into two groups, one was treated with oral sucrosomial iron (SI) and the other with intravenous ferric carboxymaltose (FCM). Patients received a single 1000 mg dose of FCM from the day after admission to rehabilitation (T1), or a 120 mg/day dose of SI from T1 until discharge (T2); after discharge, SI was reduced to 30 mg/day until the end of follow-up (T3). Hb was evaluated at T1, T2 and T3; the other hematological parameters at T1 and T3; natriuretic peptides at T1, T2 and T3; 6-minute walk test (6MWT) at T1 and T2. Folate, vitamin B12 and reticulocytes were sampled on admission. Folate deficiency was documented in 60.4% of patients. Hb increased in both groups with no significant differences between the two treatments ($p = 0.397$). The other iron metabolism parameters (sideremia, transferrin, TSAT) displayed similar behavior, showing a significant increase at T3 ($p < 0.001$) with both therapies, although the increase was faster with FCM. Ferritin – high on admission – decreased at T3 in the SI group and rose significantly in the FCM group (SI 219.5 vs. FCM 689 ng/ml $p < 0.0001$). The 6MWT increased significantly at T2, with an overlap between SI and FCM. In conclusion, the results of this study show that SI and FCM exhibit the same effectiveness on IDA; the response time to therapy of both treatments is also equally fast. SI and FCM induce a similar increase in functional capacity. The study shows that SI can be a viable alternative to FCM after cardiac surgery in terms of effectiveness and tolerability.

1. Introduction

Iron is an essential element of enzymes, cytochromes, and oxygen-carrying molecules (hemoglobin and myoglobin), due to its ability to donate and transport electrons as it changes from the trivalent ferric form to the bivalent ferrous form [1]. Consequently, cells with high energy demands, such as myocardiocytes and skeletal muscle cells, are particularly sensitive to iron deficiency. Iron deficiency (ID), frequently associated with iron deficiency anemia (IDA), is one of the most important dietary disorders, and affects about one third of the population [2]. Individuals at high risk of ID include children, the elderly, and women, especially during pregnancy and menstruation [3].

In recent years, IDA has been much investigated in patients with acute [4] and chronic [5] heart failure, with reduced, mid-range and preserved ejection fraction [6] and in outpatients [7]. Prevalence ranges from 40 to 70%, with the highest values correlating with NYHA class, reduced functional capacity, worse quality of life and the severity of heart failure. ID can occur as the result of reduced intestinal absorption, reduced mobilization by the reticuloendothelial system due to chronic inflammation, reduced renal function and, lastly, increased gastrointestinal leakage [8]. Several randomized clinical trials have shown that ID correction is associated with improved quality of life, functional capacity, NYHA class and reduced hospitalization in both chronic [9–13] and acute heart failure [14]. Meta-analysis data [15,16] indicate a

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benefit in terms of cardiovascular mortality too and major findings were confirmed in a study of outpatient chronic heart failure patients [7]. Notably, ID *per se* is associated to adverse outcome [10]; however, the positive effect of ID correction has only been demonstrated when iron is administered intravenously, with ferric carboxymaltose (FCM) recording the strongest corroborating data. Unfortunately, high-dosage oral polysaccharide iron did not improve exercise capacity, quality of life or natriuretic peptides [17], probably due to the inability to overcome the block of intestinal absorption and cell mobilization induced by hepcidin [18].

ID has recently been shown to be a marker of adverse events (re-infarction and cardiovascular mortality), both in acute coronary syndrome [19] and in individuals with documented coronary artery disease [20]. In addition, a population-based study of apparently healthy individuals, who were monitored for 10 years, found a prevalence of absolute and relative ID of 11.8% and 54.5%, and an increased risk of all-cause mortality of 90% and 30%, respectively, after adjustment for coronary risk factors [21]. These findings highlight the needing for ID treatment in other patient populations, such as those with COPD [22], primary pulmonary hypertension [23], chronic kidney disease [24] post-bariatric surgery [25] or during pregnancy [26].

Perioperative anemia represents another condition associated to an increased incidence and morbidity. In cardiac surgery patients, the higher baseline cardiovascular risk profile makes the patient more susceptible to the negative effect of anemia. A Canadian multicenter study [27] including 3500 patients showed an increased risk of adverse events (in-hospital death, stroke, acute kidney injury) in anemic patients undergoing cardiac surgery, with a baseline risk-adjusted odd ratio of 2.0; and these data were substantially confirmed by other studies [28–30]. However, intraoperative, and postoperative transfusions were found to have no apparent impact on outcome. In addition, transfusions are associated with infections, ischemic complications, longer hospital stays, higher hospital costs and increased early and late mortality [31].

Such apparent inconsistency can be explained by ID being a risk factor for increased mortality, severe adverse events and increased hospital stays after cardiac surgery, with or without anemia, with 90-day mortality increasing by 2% to 5% in patients without anemia and by 4% to 14% in patients with anemia [32]. This shows that diagnosing and treating ID, with or without associated anemia, is mandatory in these patients. Indeed, a consensus statement on the management of anemia, even after major surgery, stressed the importance of diagnosing and correcting ID [33]. However, the systematic review by Tankard et al. [34] showed that preoperative intravenous iron supplementation gave poor results. In one RCT, the use of FCM (20 mg/kg), erythropoietin alpha (40,000 IU), vitamin B12 and folic acid on the day before surgery was associated with a higher reticulocyte count, postoperative hemoglobin, fewer transfusions, and fewer adverse events, although in the latter case the reduction was not significant [35]. In an observational pilot study, Peters et al. administered a 500 mg intravenous dose of FCM in post-cardiac surgery ICU to patients with IDA and achieved a significant increase in Hb at 7 days, namely by 0.4 g/dL vs. −0.1 g/dL in untreated patients [36]. The latest guidelines on Patient Blood Management [37] drawn up based on the latest available evidence, stress how preoperative anemia, which frequently occurs in cardiac surgery, leads to an increased risk of transfusions, mortality, and morbidity. Consequently, the guidelines recommend establishing the type of anemia accurately and place great emphasis on preoperative martial therapy, which is also essential to prevent allogeneic transfusions.

To date, there are two studies in the literature on IDA correction after cardiac surgery, conducted in Cardiac Rehabilitation Units. The first study [38], confirms that absolute ID is associated with prolonged hospital stay and is more frequent in cardiac valve surgery, reasonably due to a higher prevalence of heart failure. The second study [39] compared treatment with FCM vs. iron gluconate and showed that FCM is more effective in restoring hemoglobin levels and improving functional capacity after cardiac surgery.

The aim of this study was to compare the short-term effectiveness of Sucrosomial Iron® (SI) on IDA and Hematinic Deficiencies in patients after cardiac surgery, with that of IV FCM. SI is an innovative oral iron formulation in which ferric pyrophosphate is protected by a matrix of phospholipids and sucrose esters of fatty acids envelope (*sucrosome*). SI was chosen for oral iron supplementation because of its unique intestinal absorption properties which overcome the block induced by hepcidin, even in patients with heart failure [40,41]. In addition, a recent study demonstrates the positive impact of SI at 60 mg/day, 30 days before surgery, which increases baseline Hb level and reduces postoperative negative fluctuations [42]. The secondary goal was to evaluate the impact of the two treatments on functional capacity and to obtain a snapshot of the blood levels of folate and vitamin B 12 early after cardiac surgery.

2. Methods

2.1. Study design

Single-center retrospective observational study conducted on patients with iron deficiency anemia admitted to the Cardiac Rehabilitation Unit of the Civil Hospital of Cecina after cardiac surgery for inpatient rehabilitation treatment after cardiac surgery. In the study, patients treated with SI were the case group and those treated with FCM were the control group. All patients gave informed consent at hospital admission.

3. Patients

The study includes 106 consecutive patients admitted to the Cardiac Rehabilitation Unit of the Civil Hospital of Cecina from December 2018 to December 2020. After cardiac surgery, all patients were admitted to our unit for an in-hospital short comprehensive cardiac rehabilitation program. Briefly, cardiac rehabilitation program consisted of breathing exercises during the first few days of hospitalization, using both respiratory rehabilitation techniques and incentive spirometers, and successively of it consisted of training sessions on a stationary bike from 0 (zero) load up to 25–30 W, with telemetry oxygen saturation and electrocardiograph monitoring during exercise session.

Functional ID was defined as TSAT $< 20\%$ and serum ferritin ≥ 100 mg/l; absolute ID was defined as serum ferritin ≤ 100 ng/ml. Anemia was diagnosed according to the World Health Organization definition (Hb $<$ 13 g/dl in men and $\leq$ 12 g/dl in women). The dose of FCM 1000 mg, diluted in sterile 250 ml 0.9% sodium chloride solution, was administered in 30 '; the patients were subsequently observed for adverse effects for at least 30 min.

Inclusion criteria were as follows: Hb $\leq$ 12 g/dl in women and $\leq$ 13 g/dl in men, and transferrin saturation [TSAT] $\leq 20\%$, and left ventricular ejection fraction (LVEF) $\geq 45\%$. Exclusion criteria were as follows: age $<$ 18 years, pregnancy, patient needed blood transfusions during hospital stay, acute and chronic renal failure, iron allergy/intolerance and inability to perform the six-minute walk test (6MWT). The 6MWT procedure have been conducted according to the American Thoracic Society statement [43]. Patients with cardiac prosthesis-related hemolysis (elevated unconjugated bilirubin ad lactate dehydrogenase at admission), were also excluded.

Patients who meet the inclusion criteria, were alternatively treated with IV FCM or SI. Patients were divided into two groups: 52 were treated with FCM and 54 with SI. Study design prescribed a single 1000-mg dose of FCM at T1 (8–10 days after surgery) or a daily 120-mg dose of SI from T1 until T2 (upon discharge 10 days after T1); SI was then reduced to 30 mg daily until T3 (follow-up, 10 days after T2). Fig. 1 shows the treatment scheme.

The following variables were collected and stored in anonymous form, in a database for both groups:

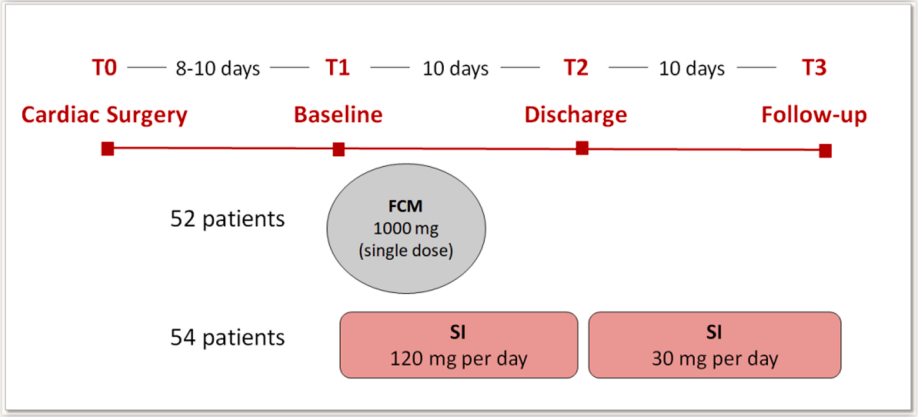

Fig. 1. Treatment scheme.

1. Demographic, anthropometric and baseline clinical data: age, height, weight, body mass index, comorbidities such as diabetes and hypertension, and left ventricular ejection fraction (LVEF). 6MWT was performed on admission and discharge (T1 and T2), after martial therapy.
2. The following biochemical data were collected on admission: natriuretic peptides, hemoglobin, serum iron, transferrin levels, ferritin, TSAT, creatinine, C-reactive protein (CRP), folate, reticulocytes, vitamin B 12, both on admission and discharge (after iron therapy). For some variables (hemoglobin, C-reactive protein and NT-proBNP) repeated measurements were taken at 3 points in time (T1, T2, T3); for others (sideremia, transferrin, ferritin, TSAT and creatinine) repeated measurements were taken at 2 points in time (T1 and T3). During the study, the reference analysis laboratory changed natriuretic peptide measurement method from BNP measurement (76 patients) to NT-proBNP measurement (30 patients). The two variables were analyzed separately because the two set of data are not comparable. Likewise, reticulocytes, folate, and vitamin B12 were only measured in patient admitted in 2020.
3. Effectiveness measures included changes from baseline Hb, hematological parameters, natriuretic peptides, C-reactive protein, and 6-minute walk distance (6MWT).

3.1. Statistical analysis

Values are reported as mean ± standard deviation, median and interquartile range, or proportion, depending on their distributions; consequently, the two treatment groups were compared using the two-tailed *t*-test for independent samples, the non-parametric Mann-Whitney test, or the chi-square test with Yates' correction.

The effect of time and treatment on the variables of interest was analyzed using a two-way analysis of variance for repeated measures, checking the assumptions of equal variance with Levene's test and the assumption of sphericity with Mauchly's test; when the assumption of sphericity was found to have been violated, the Greenhouse-Geisser correction (eGG) was used if $e < 0.75$, or the Huynd-Feldt correction (eHF) if $e \geq 0.75$. For non-Gaussian longitudinal variables, the significance of the effects of time, treatment and their interaction were assessed with a robust method based on the 20% trimmed mean; the effect of time in each treatment group was assessed with the non-parametric Friedman test.

Post-hoc comparisons were carried out using the non-parametric Mann-Whitney and Wilcoxon tests. All post-hoc comparisons were performed using the Bonferroni correction. Correlations between ferritin and CRP measurements were assessed by calculating the non-parametric Spearman's rank correlation coefficient (RHO). A p-value of < 0.05 was considered statistically significant. All analyses were carried out using the statistical software R.

4. Results

Table 1 shows the clinical data and hematological parameters collected on admission to the cardiac rehabilitation unit. The two groups were comparable (SI vs FCM) in terms of age (68.9 ± 11. vs. 70.04 ± 12.4), sex distribution (males 72.22 vs.61.54 %), comorbidities and ejection fraction (SI vs FCM: 52.96 ± 7.35 vs. 53.88 ± 4.77%).

The two treatment groups showed no significant difference at baseline in terms of demographics, comorbidity, left ventricular function, hematological parameters, creatinine, natriuretic peptides, inflammatory status, reticulocyte count, folate, and vitamin B12 (Table 1). Regarding antiplatelet and anticoagulant therapy, as per protocol, all patients with valve prostheses were treated with warfarin for at least the first 3 months after surgery. CABG patients received only one antiplatelet drug unless PCI was associated; in which case the antiplatelet therapy is twofold (only 1 case in this cohort). All patients with CABG + Heart Valve Surgery were treated with warfarin and aspirin.

Regarding changes in Hb, the two-way repeated-measure analysis of variance showed no significant difference associated with the type of martial therapy ($p = 0.397$). On the other hand, a significant variation over time ($p < 0.001$) and a significant difference due to the interaction between time and treatment ($p = 0.002$) was observed. An analysis of Hb behavior in diabetic patients, in patients with hypertension, men and women, showed comparable results and confirmed that FCM and SI have a similar effect on the increase in Hb values (Hb-T3 FCM vs. SI, 12.53 ± 1.28 vs. 11.99 ± 1.27), suggesting that these treatments are statistically equivalent (Table 1S).

Serum iron values also increased in both treatment groups and showed significant variation over time ($p < 0.001$); although a significant difference ($p < 0.001$) was observed between the two groups at T3 in favor of FCM (FCM vs. SI: 67.02 ± 27.2 vs. 53.59 ± 15.34. $p < 0.0001$). The behavior of serum iron in men, women and in patients with hypertension is similar; conversely, the difference between FCM and SI does not reach statistical significance in diabetic patients (63.62 ± 19.27 vs. 50.88 ± 14.61. $p = 0.173$) (Table 2S).

Transferrin showed a significant increase over time; however, there is no statistically significant difference between FCM and SI at T3 ($p = 0.0555$). Notably, Transferrin levels were statistically significant over time for all subgroups analyzed (Table 3S). Transferrin saturation (TSAT) improved significantly ($p < 0.001$) from baseline values in both groups. At T3, however, the increase is greater in the group treated with FCM (FCM vs. SI: 0.24 ± 0.1 vs. 0.18 ± 0.05, $p < 0.001$). The evolution of TSAT is comparable in the subgroups analyzed too (Table 4S).

Lastly, the two-way analysis of variance shows a significant change

Table 1
Clinical and biochemical characteristics of study population at baseline.

	Total Population (n = 106)	FCM (n = 52)	SI (n = 54)	*P* (FCM vs. SI)
Age	69.46 ± 11.75	70.04-± 12.42	68.91 ± 11.16	0.6235
BMI	27.9 ± 5.8	27.4 ± 6	28.1 ± 6	0.25
Diabetes	32 (30.19 %)	16 (30.77 %)	16 (29.63 %)	1
Hypertension	77 (72.64 %)	37 (71.15 %)	40 (74.07 %)	0.9051
Male	71 (66.98 %)	32 (61.54 %)	39 (72.22 %)	0.3357
Hemoglobin (g/dl) T1	10.03 ± 1.55	10.06 ± 1.36	10.19 ± 1.1	0.8573
Serum iron (mg/dl) T1	31.58 ± 9.59	31.42 ± 8.78	31.72 ± 10.4	0,873
Transferrin (mg/dl) T1	187.96 ± 40.7	180.19 ± 34.42	195.44 ± 45.01	0.0523
TSAT T1	0.12 ± 0.04	0.12 ± 0.04	0.12 +/- 0.04	0.5296
Ferritin (ng/ml) T1	394.5 [230.75–635]	386 [218.75–604.25]	411 [281.75–642.75]	0.3089
Creatinine (mg/dl) T1	1.02 ± 0.34	1.04 ± 0.36	0.99 ± 0.32	0.4544
Reticulocytes - T1 (missing = 61)	99.58 ± 31.31	99.86 ± 33.01	99.3 ± 30.34	0.9531
Folate - T1 (missing = 61)	4 [2–8.4]	3.7 [1.92–11.5]	4 [2.25–7.6]	0.9909
Vitamin B12 - T1 (missing = 61)	450 [333–620]	449.5 [340.5–702.25]	456 [332–595.5]	0.6335
LVEF (%) - T1	53.42 ± 6.21	53.88 ± 4.77	52.96 ± 7.35	0.4443
6MWT (m) T1 (missing = 6)	245.03 ± 134.74	243.02 ± 137.08	247.04 ± 133,716	0.8823
BNP (pg/ml) T1 (missing = 30)	242 [131.5–409.5]	238 [142–442]	246 [108–403]	0.3286
NT-proBNP (pg/ml) T1 (missing = 76)	1581 [950.2–2786.2]	1328 [878–2300]	1744 [1056–3071]	0.4864
CRP (mg/dl) T1	4.71 [3.05–6.8]	4.94 [2.96–7.44]	4.58 [3.08–6.29]	0.4616
CABG	37 (34.9 %)	18 (34.6%)	19 (35.2%)	–
Heart Valve	47 (44.3 %)	23 (46.1 %)	24 (44.4 %)	–
CABG + Heart Valve	22 (20.8 %)	10 (19.3%)	11 (20.4%)	–

Table 2
Hemoglobin and other hematinic parameters at baseline (T1), discharge (T2) and follow-up (T3).

	T1	T2	T3	*p* (FCM vs SI)
Hb SI (g/dl)	10.19 ± 1.10	10.82 ± 1.15	11.99 ± 1.27	T1: p = 0.8573
Hb FCM (g/dl)	10.06 ± 1.36	10.97 ± 1.37	12.53 ± 1.28	T2: p = 0.5509
				T3: p = 0.0299
Serum iron SI (mg/dl)	31.72 ± 10.40	–	53.59 ± 15.34	T1: p = 0.873
Serum iron FCM (mg/dl)	31.42 ± 8.78	–	67.02 ± 27.20	T3: p = 0.0026
Transferrin SI (mg/dl)	195.44 ± 45.01	–	218.35 ± 41.26	T1: p = 0.0523
Transferrin FCM (mg/dl)	180.19 ± 34.42	–	204.00 ± 34.85	T3: p = 0.0555
Transferrin Saturation SI	0.12 ± 0.04	–	0.18 ± 0.05	T1: p = 0.5296
Transferrin Saturation FCM	0.12 ± 0.04	–	0.24 ± 0.10	T3: p = 0.0003
Ferritin SI (ng/ml)	411 [281.75–642.75]	–	219.5 [128.25–417.25]	T1: p = 0.3089
Ferritin FCM (ng/ml)	386 [218.75–604.25]	–	689 [514.25–977.75]	T3: p < 0.0001

Table 3
Creatinine at baseline (T1) and follow-up (T3); natriuretic peptides and CRP at baseline (T1), discharge (T2) and follow-up (T3). 6MWT at baseline (T1) and discharge (T2).

	T1	T2	T3	SI vs. FCM
Creatinine SI (mg/dl)	0.99 ± 0.32	–	1.03 ± 0.26	NS p: 0.3
Creatinine FCM (mg/dl)	1.04 ± 0.36	–	1.1– ± 0.36	
BNP SI (pg/ml), n:33	246 [138–401]	144 [80–227]	131 [75–193]	NS p: 0.398
BNP FCM (pg/ml), n:34	227.5 [145.5–524.5]	159.5 [108.5–347.75]	128.5 [85.5–241.25]	
NT-proBNP SI (pg/ml), n:15	1744 [1056–3071]	971 [659–1601]	745 [310–833]	NS p: 0.682
NT-proBNP FCM (pg/ml), n:15	1328 [878–2300]	752 [526–1319.5]	686 [412–1819]	
CRP SI (mg/dl)	4.58 [3.11–6.27]	1.31 [0.86–2.31]	0.65 [0.36–1.31]	NS p: 0.468
CRP FCM (mg/dl)	4.91 [2.96–7.1]	1.35 [0.92–2.23]	0.86 [0.36–1.73]	
6MWT SI (m)	248.58 ± 135.75	349.12 ± 148.22		NS p: 0.915
6MWT FCM (m)	245.65 ± 138.1	346.35 ± 121.51		

in ferritin over time; however, the two treatments lead to opposite changes. Ferritin increased from baseline in the FCM group, and decreased in the SI group, with a significant difference ($p < 0.001$) between the two treatments at T3 (FCM vs SI: 689 [514.25–977.75] vs. 219.5 [128.25–417.25]). The evolution of ferritin levels is comparable in the subgroups analyses (Table 5S).

Table 2 shows the Hb values and hematological parameters in the two treatment groups, and Fig. 2. shows the corresponding charts

Two-way repeated-measure analysis of variance showed a significant change over time in creatinine ($p = 0.034$), but no significant difference due to treatment ($p = 0.3$), or to the interaction between time and treatment ($p = 0.585$). At T3 the values, no significant difference in creatinine levels was observed.

A separate analysis was carried out for BNP (n = 76) and for NT-proBNP (n = 30). A trend in reduction was observed for both treatment cohorts without reaching statistical significance.

Two-way repeated-measure analysis of variance showed significant changes over time ($p < 0.001$) in CRP levels, but no significant differences due to the interaction between time and treatment ($p = 0.708$), or to treatment ($p = 0.468$) were observed. The change over time was significant for the two individual treatments (FCM: $p12 < 0.001$, $p13 < 0.001$, $p23 = 0.003$; SI: $p12 < 0.001$, $p13 < 0.001$, $p23 < 0.003$).

The non-parametric Spearman's rank correlation coefficients between Ferritin and CRP measurements were calculated. There is a weak correlation between the reduction in CRP and the reduction in Ferritin in the whole sample. However, when the two subgroups (FCM and SI) are considered separately, all statistical significance is lost, even after data is normalized.

Lastly, a significant change over time ($p < 0.001$) in 6MWT was reported for both treatments, but no significant difference due to the

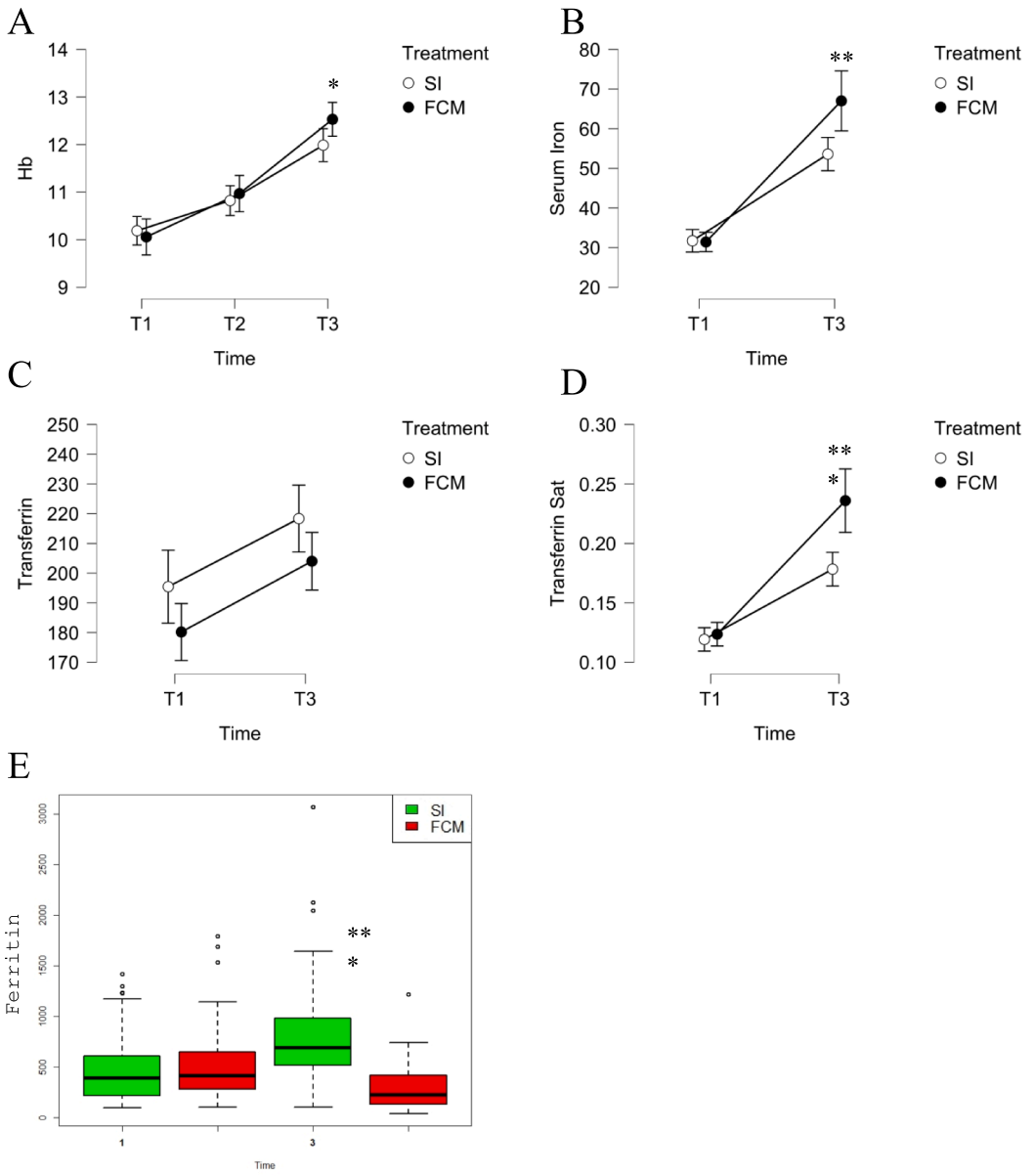

Fig. 2. Hemoglobin and other hematinic parameters at baseline (T1), discharge (T2) and follow-up (T3).

interaction between time and treatment (p = 0.992), or to treatment (p = 0.915) was found. Please note that the 6-minute walk test is missing in 6 patients: 3 patients were unable to perform it, 2 completed the 6MWT only on discharge and 1 patient refused it.

Table 3 shows the values for creatinine, PCR, natriuretic peptides and 6MWT and Fig. 3 shows the corresponding charts.

Lastly, these data confirm that folate deficiency is relatively frequent after cardiac surgery, affecting 60.4% of patients; conversely, vitamin B12 deficiency affects only 6.6% of surgical patients. Bone marrow response to IDA is satisfactory with reticulocyte values above normal range in 57.8% of patients examined and within normal range in 47.8% of patients.

Safety. SI did not induce any gastrointestinal symptoms despite the high dosage during hospital stay. FCM administration was discontinued due to an urticarial rash in one patient who had a history of multiple allergies. No patients underwent blood transfusions.

5. Discussion

This study aimed at comparing the effectiveness of two iron supplements in patients with IDA after cardiac surgery: the major finding is their comparable effectiveness in increasing Hb and resolving IDA, especially considering that one treatment was administered orally (SI) and the other intravenously (FCM). Treatment effectiveness is unchanged in the subgroups analyzed (males, females, patients with hypertension and with diabetes, Supplement data).

Oral iron therapy had been found to be significantly inferior [17] to FCM in cardiology so far. As a matter of fact, the latest Guidelines for the treatment of heart failure [44] and blood management in cardiac surgery [37] point out that only intravenous iron should be used, as these conditions are associated with a reduced intestinal absorption of 'conventional' oral iron.

Anemia is a condition that is associated with adverse events especially after cardiac surgery, when the higher baseline cardiovascular risk profile makes the patient more susceptible to the negative effect of anemia [27–30]. Therefore, the current Guidelines emphasize the

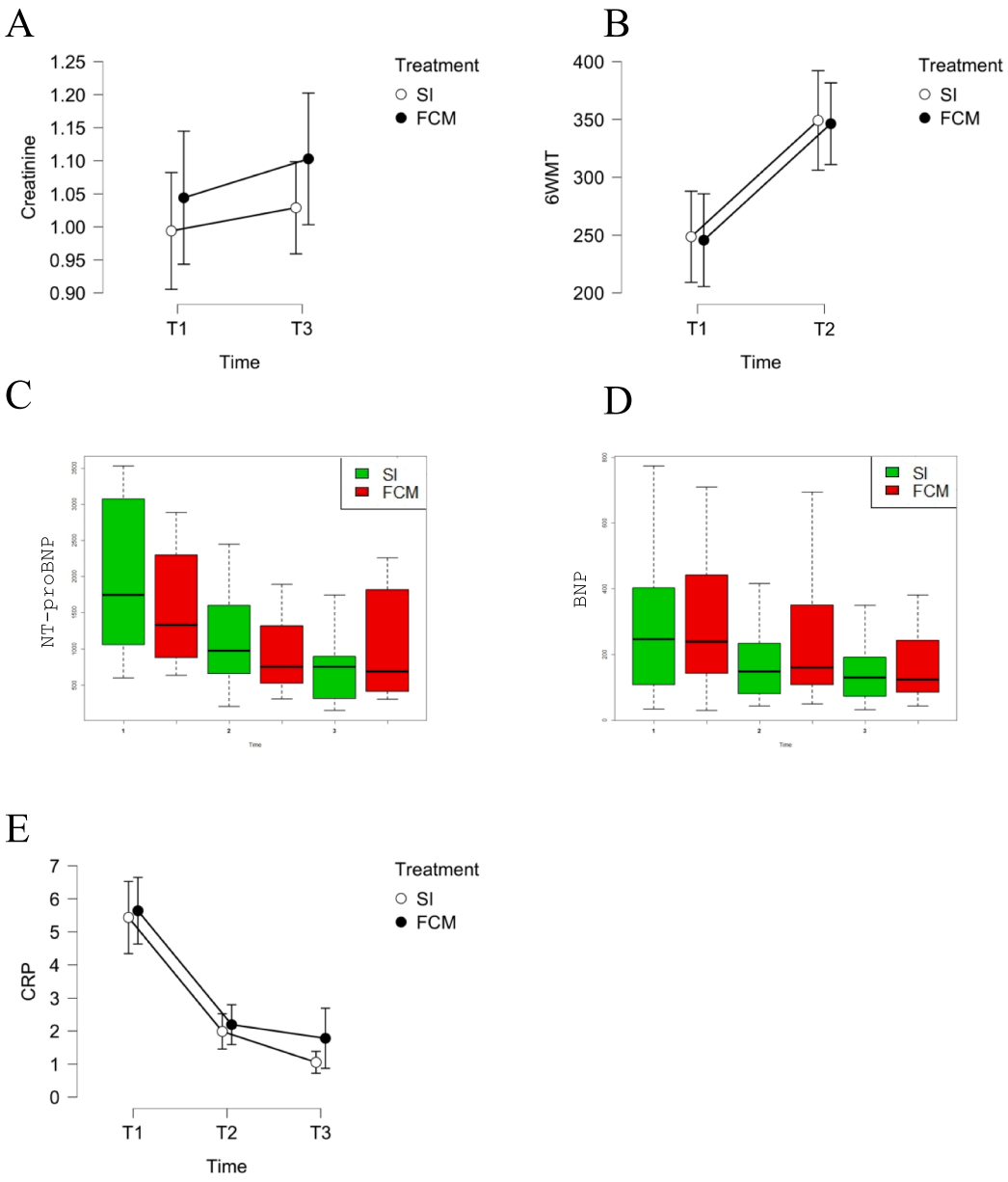

Fig. 3. Creatinine levels at baseline (T1) and follow-up (T3); natriuretic peptides and CRP at baseline (T1), discharge (T2) and follow-up (T3). 6MWT at baseline (T1) and discharge (T2).

importance of establishing the type of anemia and correcting it by administering iron [37], when necessary. Although Guidelines refers fundamentally to the preoperative phase, there is no reason to believe that the detrimental effects of anemia will wear off after surgery. Furthermore, absolute ID is associated with prolonged hospital stay, at least after heart valve surgery [38]. Indeed, in clinical practice, the IDA is routinely assessed and corrected after cardiac surgery, resulting in significant clinical benefits (the faster the IDA is corrected, the faster the improvement in functional capacity) [39].

Therefore, in the context of a routine correction of IDA after cardiac surgery, we aimed at verifying whether there were differences on the haematological and clinical-instrumental parameters usually used during the hospitalization in Cardiac Rehabilitation, comparing the oral SI to FCM therapy, which is the gold standard of IDA therapy in Cardiology. The present data confirm that SI is a valid and effective option for increasing Hb and iron balance in general, at least after cardiac surgery. Lastly, it is worth noting how Hb levels recovered very quickly with SI (twenty days), a speed comparable to that observed in intravenous therapy. A study on the treatment of IDA in patients with ulcerative colitis [45] had reached similar conclusions, although the term of comparison there was a 12-week treatment with SI (8 weeks at 60 mg/day and 4 weeks at 30 mg/day). This shows that SI absorption is not only effective in patients with phlogosis, such as patients after cardiac surgery or with ulcerative colitis, but also shows a correlation in terms of speed with the dose used (120 mg/day vs. 60 mg/day). Notably, the dose of SI changed during the treatment, obtaining good results. Moreover, Giordano et al. [46] used a dose of 120 mg of sucrosomial iron, obtaining an increase of 1 g/dL of Hemoglobin in 9 days. In this study, the same dose of Giordano's study [45] was used since the first day after surgery to obtain a rapid increase of hemoglobin, and then it was reduced to 30 mg/day to ensure a maintenance dose of iron.

The favorable results with SI are due to its structure, as sucrosome prevents gastric inactivation, allowing iron to be transported into the intestinal mucosa with a higher absorption rate than other iron salts [47]. Furthermore, these patients were very often treated with proton-pump inhibitors, due to recent surgery and coexisting antiplatelet,

antithrombotic, or anticoagulant therapy, and their use reduced the absorption of iron salts [8]. The efficacy of SI also in these patients is further evidence of the high enteric absorption of SI.

Regarding other hematological parameters (sideremia and TSAT), both treatments induced a significant increase. While the increase seems faster with FCM at T3, this nonetheless did not translate into a significant difference in Hb levels between SI and FCM at the end of the study. The improvement in these parameters further confirms the excellent enteric absorption of SI.

Ferritin deserves separate discussion. In addition to being an iron-storage protein, it is a marker of inflammation and cellular damage [48]. Moreover, serum ferritin is inversely correlated with the levels of antioxidant vitamins and CRP and is used to assess clinical outcomes that are presumed to be caused by iron-driven oxidative stress [49]. Consequently, high ferritin values are common after cardiac surgery [38,39,50]. Besides the activation of inflammatory response during cardiopulmonary bypass, hemolysis, peripheral muscle damage and ischemia–reperfusion injury are also causes of hyperferritinemia, which seems to correlate with an adverse outcome [51].

Ferritin levels were high at baseline and changed significantly in opposite directions over time: they increased from baseline in the FCM group, whereas they fell in the SI group, with a significant difference (FCM vs SI: 689 [514.25–977.75] vs. 219.5 [128.25–417.25] $p < 0.001$). Although the change of ferritin is consistent with the reduction in CRP only in SI-treated patients, an analysis of the non-parametric Spearman's rank correlation coefficients between Ferritin and CRP measurements in individual subgroups shows that all statistical significance is lost, even after data is normalized. This can be explained by CRP dropping in both the SI and FCM group at T3 mainly due to the improved post-surgical inflammatory state. Therefore, the different changes of ferritin were due to the different mechanism of action of the two iron treatments: intravenous administration of 1000 mg of FCM rapidly increases blood levels of iron by stimulating the deposition of iron in the form of ferritin, whereas SI leads to a smaller increase in iron and can only support Hb synthesis in bone marrow [45]. In addition, administering intravenous iron can have an inflammatory effect, at least in patients with IDA and chronic kidney disease, by inducing pro-inflammatory activation of macrophages through the release of cytokines and other inflammatory mediators [52].

The study also evaluated the blood levels of two water-soluble vitamins essential for erythropoiesis: vitamin B12 and folic acid. Reduced levels of the two vitamins (especially of folate, in 60.4% of patients) are significantly more frequent in our case series than in the literature. In the cohort of Hugh et al. [53] only 6.6% of patients had folate/B12 deficiency. This shows that testing for and correcting vitamin deficiency is mandatory after cardiac surgery.

That IDA strongly affect functional capacity on admission to cardiac rehabilitation, is a long-established fact, denoted by a shorter distance walked during the 6-minute walk test [38]. The pathophysiological basis for this lies in the central action, at cardiac level, but also at peripheral level, on skeletal muscle, induced by iron deficiency. As a matter of fact, mitochondrial function in myocardiocytes with IDA is reduced with impaired ATP-bound respiration and reduced respiratory reserve; maximum velocity is reduced during systole and diastole because of reduced ATP production [54]. In short, iron deficiency leads to reduced activity of citric acid cycle enzymes, of protective enzymes against reactive oxygen species (ROS) and reduced mitochondrial O_2 consumption. At the level of skeletal muscle, administering intravenous iron isomaltoside increases skeletal muscle energy, as shown by shorter recovery half-lives of phosphocreatine and ATP and reduced dyspnea (Borg score), before inducing a significant increase in Hb [55]. This shows that improved mitochondrial function in skeletal muscle leads to increased energy and consequent functional capacity [56,57].

Therefore, it is hardly surprising that FCM was found to be more effective than iron gluconate in significantly increasing the 6MWT distance [39] during cardiac rehabilitation program after cardiac surgery; the improved bioavailability of FCM enables faster recovery of cardiac and skeletal muscle mitochondrial function. Conversely, SI treatment demonstrated an identical increase in the distance walked during the walk test at the end of hospital stay (T2) for SI and FCM (349.12 ± 148.22 vs. 346.35 ± 121.51, p: 0.915). This is a significant finding since oral iron demonstrated effectiveness in comparison to FCM in inducing an improvement in functional capacity; particularly considering that FCM was the only type of iron recommended by the ESC Guidelines in acute and chronic heart failure [44] so far. This effect highlights again the unique enteric absorption of SI, which bypasses the DMT-1 (Divalent metal transporter-1) ferroportin axis and is absorbed via vesicles through transcellular and paracellular pathways, as well as via microfold cells (M cells), into lymphatic circulation [58].

Interestingly, natriuretic peptide data were slightly elevated on admission to cardiac rehabilitation unit and decreased at the end of the observation period (T3) with no significant difference between the SI and FCM groups. At first glance, these findings seemed in line with a comparative study comparing iron gluconate and FCM [39]. However, in the Nugara et al. [39] case series, NT-proBNP was significantly higher in the FCM group on admission (3848 vs. 1335 ng/ml), likely suggesting that those patients were more hemodynamically compromised and that FCM proved to be more effective in reducing natriuretic peptide. Conversely, in our cohort of patients, the reduction is homogeneous and overlapping in the two groups.

Several limitations should be acknowledged. The relatively small sample size limits the generalization of conclusions. In addition, this is a retrospective single-center study and has all the limitations associated with this type of study, such as the reference analysis laboratory switching to a different natriuretic peptide analysis (BNP or NT-proBNP), and the dosage of folate, vitamin B12 and reticulocytes not being available for all patients. In addition, measuring certain markers, such as hepcidin [18], cytokines [46], fibroblast growth factor (FGF)–23 and phosphatemia [59,60], would have allowed a more exhaustive analysis of the pathophysiology of the absorption of the two types of iron after cardiac surgery, lending more significance to our study. In addition, the observation period of the study is not long enough to draw any final conclusions on the medium-to-long-term effectiveness of the two treatments. Moreover, postoperative intensive care was performed in different centers with potential bias in perioperative treatment strategy. Finally, the lack of a control group without treatment should be acknowledged, limiting conclusions to the different treatment groups only, but not on any benefit of treatment itself.

In conclusion, this study showed that, in IDA patients after cardiac surgery, SI and FCM administration had similar effectiveness on key hematological parameters. The rapid response to treatment in both treatment groups might support the choice of oral supplementation, which is safe and avoid intravenous administration. In addition, SI administration showed a significant improvement in functional capacity as measured by the 6MWT. In addition, SI administration demonstrated high tolerability with no side effects, albeit at a high dose of 120 mg/day, at least during hospitalization. Undoubtedly, double-blind, randomized clinical trials of longer duration are eagerly awaited in order to confirm the effectiveness of SI administration in patients after cardiac surgery and in other cohorts of patients (i.e. heart failure patients, elderly, frail).

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Author's contributions.

VE contributed to the conception of the work. VE and GF drafted the manuscript. VE, IG, DLA, PM, MP, CG, DAA and GF contributed to the acquisition, analysis, and interpretation of data for the work. VE, IG, VC and GF critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101038.

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