Original article

Benefits of pre-operative oral Sucrosomial® iron supplementation in cardiac surgery: influence of patient's baseline hemoglobin and gender

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Background - The prevalence of low pre-operative hemoglobin (Hb) among cardiac surgery patients is high. As iron homeostasis is often impaired in these patients, restoration of iron availability might over-ride iron-restricted erythropoiesis. This post-hoc analysis of a previously published, large, randomized clinical trial (ClincalTrials.gov NCT03560687; n=1,000) assesses which sub-cohort of patients benefits the most from pre-operative Hb optimization with oral Sucrosomial® iron.

Materials and methods - Patients without baseline Hb (n=349) or receiving >5 red blood cell units (n=57) were excluded from the study. Data from the remaining 594 were reanalyzed according to treatment, baseline anemia (Hb <13 g/dL) or gender. Patients (pt) received a one-month course of 60 mg/day Sucrosomial® iron (Iron group, n=309) or routine care (Control group, n=285) prior to elective cardiac surgery. Main end-point variables were increase in Hb from randomization to hospital admission, transfusion requirements, and cost-effectiveness of Sucrosomial® iron administration.

Results - At hospital admission, Hb had increased 0.7 g/dL and 0.1 g/dL, for Iron and Control groups, respectively (p<0.001), with no gender-related differences, leading to a decrease in transfusion rate (30 *vs* 59%, respectively; p<0.001) and transfusion index (0.5 units/patient *vs* 1.2 units/pt, respectively; p<0.001). Sucrosomial® iron administration was well-tolerated, and yielded cost-savings of €92/pt (p<0.001), particularly in those presenting with baseline Hb <13 g/dL.

Conclusions - This post-hoc analysis confirms pre-operative Sucrosomial® iron administration is a safe and cost-effective strategy to increase pre-operative Hb and decrease transfusion requirements in elective cardiac surgery, especially in those anemic at baseline.

Keywords: *cardiac surgery, pre-operative anemia, iron supplementation, blood transfusion, patient blood management.*

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INTRODUCTION

Today, blood loss and blood transfusion are recognized as representing a problem in heart surgery[1-5]. It took pioneers many years to finally convince the scientific community

that blood issues, and not just transfusions, should receive attention[6]. The generalized implementation of restrictive transfusion thresholds (Hb 7-8 g/dL) in cardiac surgery patients has significantly reduced their transfusion requirements, both in the percentage of patients receiving transfusion and in the number of transfused units. However, pre-operative optimization of erythropoiesis is still required to avoid reaching such transfusion thresholds. This elusive goal is behind every study concerning erythropoietin and iron administration, whether this is explicitly stated or not. Only in cases in which the aorta is damaged during surgery will the resultant massive hemorrhage shift the attention of the medical team. However, this fatal or nearly fatal event is rare, and most surgeries are carried out without major acute adverse events. If Patient Blood Management principles are followed[7], the patient usually has a high hemoglobin (Hb) concentration when surgery begins, so there is a safe margin before the threshold at which transfusion is required is reached.

Planning a clinical study of a "real-world" population, and so increasing the applicability of its findings, should be considered as study strength and contributes to the high profile of the research. But it might introduce a bias that could mislead everyday practice: is the "one size fits all" strategy appropriate when dealing with blood management? And which sub-cohort of patients benefits the most from Hb optimization? Those whose Hb concentration is normal or those with borderline values? Patients who are overtly anemic? And, indeed, what do we consider a "normal" Hb concentration to be in the context of heart surgery[8-10]?

In spite of the growing number of articles published on the subject[11-13], these questions continue to be raised among the scientific community. This suggests that we must go back and revisit the dataset of our most recent and by far the largest study[13] and adopt a fresh approach. Although the Hb concentration of 13 g/dL makes sense in clinical practice, the aim of the present study is now to distinguish between patients over or under this, albeit disputable, level[4,8-10].

This post hoc analysis aims to cast some light on this still unresolved question, while maintaining sufficient statistical power to provide solid data.

MATERIALS AND METHODS

Patients

This is a post-hoc analysis of a previously published, large, randomized clinical trial conducted over two years at a single Institution (The European Hospital, Rome, Italy)[13]. The original trial protocol was approved by the local ethics Committee (EH2018-003) and registered at the ClincalTrials.gov site (NCT03560687). The study was started in November 2018 with randomization tables prepared ahead of the study. Full details are described in the related paper[13]. Briefly, patients were included if they were aged over 18 and under 90 years (y), and scheduled for elective cardiac surgery. Exclusion criteria included a baseline Hb ≥15 g/dL, any diagnosed hematological disease and/or an emergent indication for surgery.

Hemoglobin concentration on the day of enrolment was not recorded in all patients as this had not been mandatory in the original study protocol; it was, however, measured with a point-of-care device to make decisions concerning study inclusion. Patients whose baseline Hb concentration was not available from their clinical records were excluded from this post-hoc analysis. In addition, patients who were heavily transfused during their hospital stay (>5 red blood cells [RBC]) units were also excluded, as any pre-operative Hb optimization treatment would probably not compensate the patient's transfusion requirements.

Data from the remaining patients were reanalyzed using an Hb threshold of 13 g/dL to distinguish between anemic and non-anemic subjects of both genders, as recommended in a recent international consensus statement[9], thus creating four sub-cohorts. Data were also reanalyzed according to gender and treatment allocation, generating a further four sub-cohorts.

Treatment

The treatment arm received daily administration of 2 capsules of Sucrosomial® (SI) iron (Cardiosideral®, Pharmanutra, Pisa, Italy), starting 30 days before surgery. Each SI capsule contains ferric pyrophosphate (30 mg elemental iron), ascorbic acid (80 mg), vitamin B_{12} (2.5 µg), and folic acid (150 µg). The Control group received no additional pre-operative treatment.

Outcome variables

The main outcome variable was change in Hb concentration from baseline to the day before surgery. Measurements of

perioperative Hb concentrations were performed at the central institutional laboratory, archived in the patients' electronic data files, and then extracted for further calculation. The laboratory was blinded to the protocol, as were physicians and caregivers.

Secondary outcome variables included: compliance to drug administration in the 30 days before surgery, perioperative RBC mass loss, number of allogeneic packed RBC units transfused, length of intensive care unit (ICU) and hospital stay, and cost-effectiveness.

As regards perioperative RBC mass loss, Nadler's formula was used to calculate the patients' blood volume and total RBC mass was calculated by multiplying the blood volume with the corresponding hematocrit level. A factor of 0.91 was applied to correct hematocrit of peripheral blood sampling. The overall perioperative RBC mass loss at post-operative day 4 was calculated by subtracting the RBC volume on post-operative day 4 from the preoperative RBC volume, and by adding the total RBC volume transfused (1 RBC unit = approx. 165 mL of RBC). To adjust baseline differences in total RBC volume, the lost RBC volume was also analyzed as percentage of the patient's baseline total RBC mass (relative RBC mass loss)[14].

Cost-effectiveness was estimated solely in terms of the cost of drug (60€/patient) versus the savings in RBC units (220€/unit).

Transfusion protocol

Standard hospital transfusion protocol was applied in both groups, with an Hb threshold of 7 g/dL in absence of signs of oxygen delivery failure. This protocol was applied in the operation theater, ICU and on the ward, for the patient's entire hospital stay.

Statistical analysis

The original sample size calculation was based on the between-group difference in Hb concentration at hospital admission. The superiority margin was set at 0.5 g/dL. A two-sided significance level of 5% was used and power was set to 80%. Based on these assumptions, a total of 400 patients per arm were needed to test superiority. Thus, the study aimed to enroll 1,000 patients to ensure the robustness of findings. The 594 patients available for the post-hoc analysis still held solid statistical power with a superiority margin set at 0.8 g/dL, and in terms of non-inferiority were sufficient to ensure solid margins with a threshold of 0.4 g/dL.

Continuous data are expressed as means and standard deviations. Categorical data are presented as absolute values and percentages. Differences among variables in the two cohorts were assessed with unpaired Students τ-test or Kruskal-Wallis test for continuous variables, and with χ^2 test or Fisher's exact test for categorical variables, as appropriate. Differences among continuous variables on different time points were assessed by paired Students τ-test with Bonferroni correction.

In all cases, a standard probability value of <5% ($p<0.05$) was considered significant. All analysis was performed according to intention-to-treat.

SPSS version 21 (IBM Corporation, Somers, New York) and Excel 2016 (Microsoft, Redmond, Washington) software were used for data analysis.

RESULTS

Out of the initial 1,000-patient sample, 57 were excluded from the study because they had received more than 5 RBC units during hospitalization (Control group = 42; Iron group = 15), and 349 because their baseline Hb concentration had not been recorded (173 and 176, respectively) (**Figure 1**). The remaining 594 (285 and 309, respectively) underwent post-hoc analysis. A threshold of 13 g/dL was used to distinguish between anemic and non-anemic subjects to create four sub-cohorts (ICS, 2017).

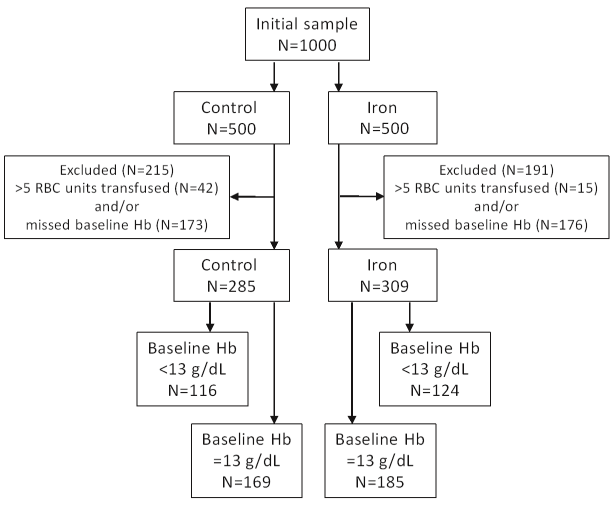

Figure 1 - Patients' disposition
Hb: Hemoglobin, RBC: red blood cells, Control: no treatment; Iron: oral sucrosomial iron (60 mg/day for 30 days).

Table I - *Demographic and clinical data from patients undergoing elective cardiac surgery according to treatment with pre-operative oral Sucrosomial® iron (60 mg elemental iron/day for 30 days; Iron group) or no treatment (Control group), and baseline hemoglobin (Hb) concentration*

Patients	All		p	Women		p	Men		p
	Control (N=285)	Iron (N=309)		Control (N=123)	Iron (N=111)		Control (N=162)	Iron (N=198)	
Gender (F/M)	123/162	111/198	**0.078**	-	-	-	-	-	-
Age (years)	70±9	66±12	**0.001**	73±8	66±13	**0.001**	69±10	65±12	**0.004**
Weight (kg)	74±13	77±14	**0.048**	67±11	69±14	0.282	80±12	81±13	0.587
Height (cm)	167±10	179±9	**0.001**	160±9	162±7	**0.001**	173±7	174±7	0.165
Intervention type (%) **Valve** **CABG** **Mixed** **Others**	 51 29 5 15	 69 11 4 16	**0.013**	 70 12 3 15	 75 3 3 19	0.077	 38 42 6 14	 65 16 4 15	**0.001**
Admission Hb≥13 g/dL, N (%)	170 (60)	240 (78)	**0.001**	53 (43)	72 (65)	**0.001**	117 (72)	168 (85)	**0.001**
Blood volume (L)	5.10±1.0	5.24±1.1	0.066	4.34±0.7	4.45±0.9	0.282	5.63±0.9	5.68±0.9	0587
Admission RBC mass (L)	1.71±0.4	1.84±0.4	**0.001**	1.41±0.2	1.52±0.2	**0.001**	1.94±0.3	2.02±0.3	**0.015**
Chest drainage 12h (mL)	402±324	343±255	**0.014**	295±190	285±233	0.718	425±289	375±262	0.090
Mortality (%)	4 (1.4)	2(0.6)	0.136	2 (1.6)	0 (0)	0.499	2 (1.2)	2 (1.0)	0.334
ICU stay (days)	3±3	2±3	**0.048**	2.6±1.8	2.3±2.3	0.345	2.3±1.6	2.0±1.1	**0.017**
Hospital stay (days)	14±7	13±6	0.090	14±7	14±8	0.851	13±7	12±5	**0.054**

In bold: statistically significant data. F: female; M: male; CABG: coronary artery bypass grafting; ICU: intensive care unit; RBC: red blood cell; h: hours; p: p-value Iron *vs* Control groups.

Data were examined to ensure that patient exclusion did not introduce a bias in favor of pre-operative treatment with oral Sucrosomial® iron. Excluded patients were younger, presented with higher Hb on admission, and had a slightly longer stay in the ICU (*Online Supplementary* **Table SI**). Mortality was higher amongst excluded patients, particularly among those who had been more heavily transfused. In fact, 16 out of the 19 deaths in the excluded patients were accounted for by the subgroup of patients receiving >5 RBC units during their hospital stay (16/57, 28%). Excluding this patient subgroup from analysis resulted in no difference in mortality rates between included and excluded patients: 6/594 (1%) *vs* 3/349 (0.9%), respectively; p=1. No differences were found in the other parameters analyzed.

We then looked for subgroup differences, either between treatment and control populations or between anemic and non-anemic sub-cohorts. To do this, demographic and clinical data from the remaining 594 patients were compared according to study group allocation and baseline Hb. This revealed minor, albeit significant, differences between groups regarding demographical parameters, which were mostly accounted for by the subgroups with baseline Hb <13 g/dL (**Table I**). There were minor differences in the type of intervention (which were no longer significant in the subgroup analysis) and shorter ICU stay in the treatment group; these remain significant only for the subgroup with baseline Hb ≥13 g/dL (**Table I**).

Overall, there were no differences in baseline concentrations between groups or subgroups, but patients from the treatment arm experienced a higher increase in Hb from baseline to admission (0.7 *vs* 0.1 g/dL, for the Iron and Control group, respectively; p<0.001). As expected, there was a bigger difference in increase in Hb in subgroups with baseline Hb <13 g/dL (0.9 *vs* 0.03 g/dL for Iron and Control arms, respectively; p<0.001) than in those with baseline Hb ≥13 g/dL (0.63 *vs* 0.13 g/dL, respectively; p<0.001). This resulted in patients from the Iron arm presenting higher Hb both on admission and throughout the observation period regardless of their baseline Hb (**Figure 2**). In addition, compared with the Control arm, more patients from the Iron arm achieved anemia correction, as defined by admission Hb ≥13 g/dL (78 *vs* 60%, respectively; p<0.001).

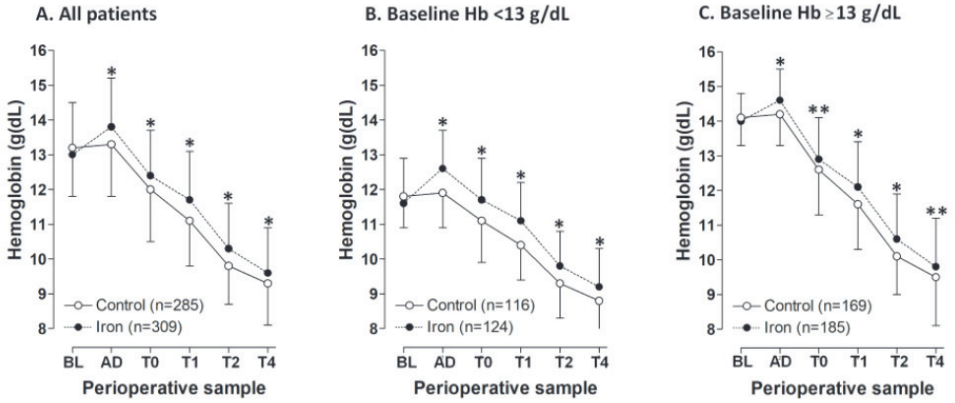

Figure 2 - Perioperative hemoglobin concentrations, according to study group and baseline hemoglobin
Control: no treatment; Iron: sucrosomial iron (60 mg/day for 30 days). BL=Base line; AD= hospital admittance; T0 immediately after operation; T1, T2, T4 postoperative day 1,2 and 4 respectively.
* p<0.001, **p<0.05, iron *vs* control.

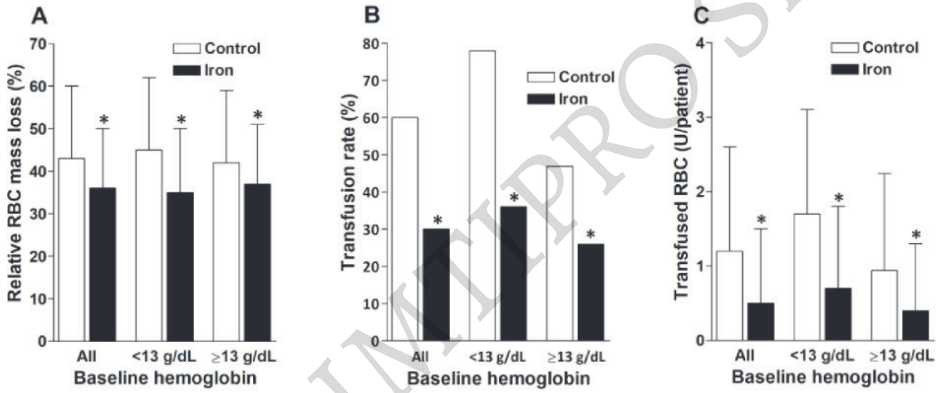

Figure 3 - Relative perioperative erythrocyte mass loss (% of admission erythrocyte mass), RBC transfusion rate (%), and transfusion index (Units/patient) according to study group and baseline hemoglobin
Control: no treatment; Iron: sucrosomial iron (60 mg/day for 30 days). *p<0.001 iron *vs* control.

Once again, this difference was accounted for by the subgroups with baseline Hb <13 g/dL (48 *vs* 3%, respectively; p<0.001) (**Table I**) with no gender-related differences (39 *vs* 55% for females and males, respectively; p=0.076). The improved Hb on admission in the Iron group translated into higher RBC mass at the same time point (**Table I**).

Relative perioperative erythrocyte mass loss (**Figure 3A**), allogeneic transfusion rate (**Figure 3B**), and RBC transfusion index (**Figure 3C**) were significantly lower in the Iron group. The improvements in these three parameters appeared to be more prominent in the <13 g/dL sub-cohort receiving pre-operative oral Sucrosomial® iron (**Figure 3**).

Finally, data were reanalyzed after gender stratification. Hb concentrations were consistently higher in men than in women throughout the entire observation period, regardless of the study arm (**Figure 4A**). However, there were no gender-related differences in the increase in Hb from baseline to admission in the iron group, regardless of baseline Hb. In contrast, virtually no change in Hb was observed in the Control group (**Figure 4B**). Once again, the effect of oral Sucrosomial® iron on increase in Hb seemed greater in the anemic subgroup (**Figure 4B**).

Relative perioperative RBC mass loss was higher in females than in males from the Control group (**Figure 5A**). Together with their lower Hb on admission

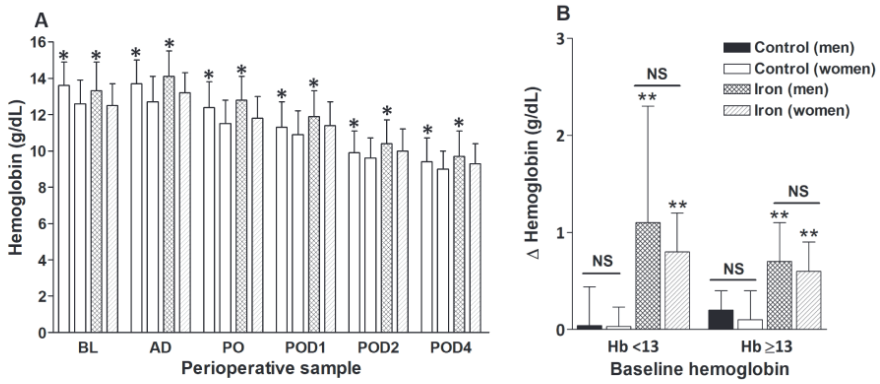

Figure 4 - Perioperative hemoglobin concentrations according to gender and treatment (A), and change from baseline to admission according to gender baseline hemoglobin and treatment (B)
*p<0.01, men *vs* women, **p<0.001, baseline *vs* admission; NS: no siginificant within group difference between men and women.

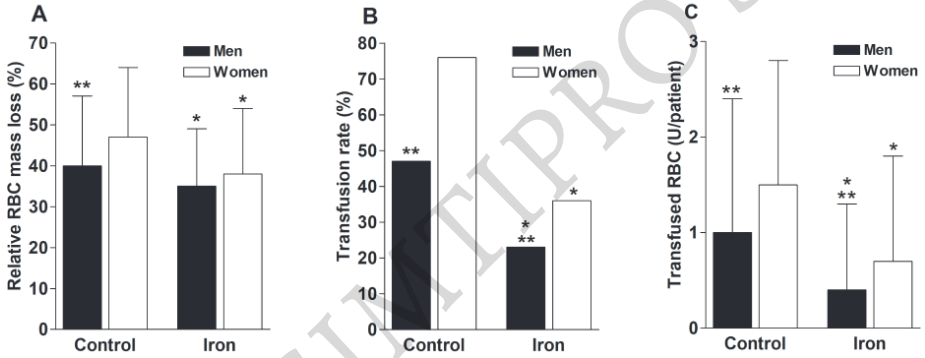

Figure 5 - Relative perioperative erythrocyte mass loss (% of admission erythrocyte mass) (A), red blood cell (RBC) transfusion rate (%) (B), and RBC transfusion index (Units/patient) (C), according to study group and baseline hemoglobin
Control: no treatment; Iron: sucrosomial iron (60 mg/day for 30 days). *p<0.01, iron *vs* control. **p<0.01, men *vs* women; NS: no significant within group difference between men and women.

(**Figure 4A**), this translated into a higher transfusion rate (**Figure 5B**) and higher transfusion index (**Figure 5C**) in the females compared to males. In the Iron group, relative perioperative RBC loss was lower than in the Control group, but there were no gender-related differences (**Figure 5A**), and this translated into lower transfusion requirements (**Figure 5B** and **C**). However, as Hb on admission in the Iron group was lower in females than in males (**Figure 4A**), transfusion rate (**Figure 5B**) and number of transfused RBC units (**Figure 5C**) were even higher in females compared to males. This identifies females as a more vulnerable subpopulation which may require a more comprehensive pre-operative strategy.

As far as the cost-effectiveness of the intervention is concerned, considering only the costs of Sucrosomial® iron supplementation and RBC transfusions, the overall cost per patient was €271±308 and €179±220, for the Control and Iron arms, respectively, yielding a cost-saving of €92 [95% CI: 49-135] per patient (p<0.001). Cost savings were higher for the anemic subgroups (€148, 95% CI: 76-220; p<0.001), compared to the non-anemic subgroups (€53, 95% CI: 2-104; p<0.040), and for females (€114, 95% CI: 46-183; p=0.001) compared to males(€68, 95% CI: 14-122; p=0.014).

DISCUSSION

In an ideal world, a particular treatment that has been seen to provide benefit for the patient could potentially be considered useful for all subjects, regardless of how slight that benefit is. In the real world, however, logistic and economic factors often mean that the treatment cannot be so widely used. Therefore, identifying populations in whom there is a greater gain helps focus on where the benefit is the most meaningful. This post-hoc analysis aimed to explore this and to identify a scale of potential benefits, with a clear identification of patients in whom treatment could become mandatory.

While substantially confirming the data of the original trial[13], this post-hoc analysis adds some intriguing insights. As a general background, given the high frequency of iron deficiency in anemic and non-anemic cardiac surgery patients[15], several studies had documented increased rates of RBC transfusion and adverse clinical outcomes[16-19]. On the other hand, there is strong evidence to support the fact that patients with low hematocrit receive more transfusions and have substantially increased post-operative morbidity, and even mortality (though this is rare)[1-5].

These observations in turn drove the idea of optimizing pre-operative erythropoiesis; this can be carried out in an outpatient setting thus allowing a timelier and more complete recovery of the RBC mass.

Data from literature show that over 30% of all patients undergoing cardiac surgery are anemic before the intervention[3-5]. When there is also chronic inflammation, such as in atherosclerotic patients, hepcidin reduces iron absorption and prevents iron recycling, resulting in iron-restricted erythropoiesis, despite normal iron stores (so-called functional iron deficiency)[20].

Since oral iron salts are associated with reduced gastrointestinal tolerance, and have been seen to be ineffective for treating iron deficiency in the context of inflammation, in these situations, it is generally recommended to give intravenous (IV) iron[21,22]. In cardiac surgery, meta-analyses have clearly shown the superiority of IV iron over oral iron, placebo or no treatment in increasing pre-operative Hb, whereas the effects on blood transfusion were not so heterogenous, probably due to the notable differences between existing RCTs in terms of populations and interventions[22,23]. This indicates that further full-scale RCTs with robust methodology are required. Moreover, the logistical challenges and cost of pre-operative IV iron administration often require surgeons working in a real-world setting to rely on transfusions rather than on Hb optimization.

In contrast with conventional oral iron products, Sucrosomial® iron is a relatively new oral iron formulation consisting of a ferric pyrophosphate core enclosed in a phospholipid membrane, which is surrounded by a sucrester matrix[24]. Intestinal absorption of SI occurs through para-cellular and trans-cellular routes (M cells), being mostly hepcidin-independent[25,26]. This gives Sucrosomial® iron a high iron bioavailability and excellent gastrointestinal tolerability[24]. These unique structural, physicochemical and pharmacokinetic characteristics generate fresh interest in oral administration, especially given the growing evidence in the literature of consistent improvements in Hb levels after 30-60 days of treatment in different clinical scenarios[24], including post-operative anemia after cardiac surgery, where oral Sucrosomial® iron exhibits the same effectiveness as IV ferric carboxymaltose[27].

Our previously published paper suggested that pre-operative oral Sucrosomial® iron administration in heart surgery was a safe (98.2% demonstrated good tolerance to the 30-day course), useful, and cost-effective strategy, which should be considered as part of standard of care[13]. Now this post-hoc analysis confirms the benefits of pre-operative administration of Sucrosomial® in terms of improved pre-operative Hb, reduced perioperative transfusion requirements, and greater cost-effectiveness. Moreover, it collects other precious information from the original dataset, showing that the scale of benefit increases when baseline Hb decreases to <13 g/dL, and identified females as a population at higher risk, possibly due to the combination of lower circulating blood volume, lower Hb, and lower iron stores.

Women have lower circulating blood volumes than men, but similar blood loss when undergoing the same procedures. Therefore, when measured as a proportion of circulating blood volume, blood loss is proportionally higher in women, and may result in higher transfusion risk with the consequent detrimental effects of further blood loss and transfusion[1]. In cardiac surgery, a 1 g/dL decrease in Hb has been shown to be independently associated

with increased transfusion requirements, increased mortality, and prolonged hospital stay[3]. In addition, the study by Blaudszun *et al.*[4] clearly describes the association between the so-called "borderline pre-operative anemia" (Hb 12-12.9 g/dL) and poor outcomes after cardiac surgery. Similar data have been published for women undergoing major abdominal surgery[28]. Consequently, women presenting with Hb 12-12.9 g/dL should have access to pre-operative Hb optimization treatment as they are at higher risk of a poor outcome, even if they are not considered anemic according to WHO definitions.

On the other hand, a large retrospective multicenter study of women with Hb <13 g/dL undergoing major elective surgery, including cardiac procedures, found that, overall, almost 90% presented abnormal iron parameters[15]. However, the relationship between iron deficiency and outcome is still controversial. Some studies have shown that iron deficiency is associated with increased transfusion requirements and fatigue[16-18], and even higher mortality in patients undergoing cardiac surgery[19]. In contrast, other studies report that iron deficiency was not independently associated with in-patient RBC transfusion[29]. Thus, it seems that iron deficiency may play a role in post-operative outcome, but the interpretation of available data is flawed by the use of different definitions of iron deficiency and the lack of stratification by gender.

It should be emphasized that a post-hoc analysis has significant intrinsic limitations, with potentially hidden selection biases. However, comparative data analysis showed that patient exclusion had not introduced a bias in favor of pre-operative treatment with oral Sucrosomial® iron (*Online Supplementary* **Table SI**). In addition, the statistical significance level reached, with a p-value often lower than 0.01- 0.001, coupled with comparative analysis of demographic and baseline parameters, suggest the findings to have good reliability.

The sole use of an Hb cut-off for prescribing iron supplementation is not the recommended approach for pre-operative stimulation of erythropoiesis, and this could also be considered a study limitation. However, certain considerations should be made:

1. A retrospective multicenter study assessing the iron status in patients undergoing cardiac procedures (n=691) found an overall prevalence of abnormal iron parameters close to 70% and 50%, in anemic and non-anemic patients, respectively[15].
2. In orthopedic surgery, iron preload has been shown to reduce the fall in Hb and in transfusion requirements, suggesting a high prevalence of iron deficiency both in anemic and in non-anemic orthopedic patients[30,31].
3. An international consensus statement suggests applying an iron preload strategy in surgical patients expected to develop severe post-operative anemia[32].
4. More recently, oral Sucrosomial® iron supplementation in orthopedic patients with Hb 13-14 g/dL and ferritin <100 ng/mL was shown to reduce the post-operative fall in Hb, transfusion requirements, and hospital length of stay[33].

As determination of iron status was not standard practice at our Institution, based on the above-mentioned data from orthopedic patients, and to keep the trial as simple as possible, decisions on iron supplementation were based on an Hb cut-off. In forthcoming studies, assessment of iron status will be included in the protocol.

CONCLUSIONS

Pre-operative oral Sucrosomial® iron administration is confirmed as a safe, well-tolerated, and cost-effective strategy to increase pre-operative Hb and decrease transfusion requirements in elective heart surgery, with a significantly higher expected benefit in anemic patients, as defined by a baseline Hb <13 g/dL for both genders. A larger confirmatory trial with prolonged follow-up is warranted.

AUTHORSHIP CONTRIBUTIONS

All Authors contributed to the study design. LW wrote the paper and performed the statistical analysis.

The Authors declare no conflicts of interest.

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