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# Preoperative Sucrosomial Iron Supplementation Increases Haemoglobin and Reduces Transfusion Requirements in Elective Heart Surgery Patients: A Prospective Randomized Study.

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## ABSTRACT

**Background: Low preoperative haemoglobin is frequently observed in heart surgery patients and is associated with a significant decrease in haemoglobin between post-operative days 2 and 3, known as haemoglobin drift. Overall, these patients tend to receive many RBC transfusions. Since iron homeostasis is often impaired in these patients, restoration of iron availability might override iron-restricted erythropoiesis. However, reduced tolerance to oral iron salts has limited this strategy to intravenous iron administration.**

**Study Design and Methods: The purpose of this study was to assess whether preoperative supplementation with oral sucrosomial iron, a new iron-delivery technology with improved tolerance and bioavailability, might be an effective strategy for this patient population. One thousand consecutive patients were randomized and received either a one-month course of sucrosomial iron (60 mg/day) or no treatment prior to elective heart surgery at a**


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**single high-volume centre (ClinicalTrials.gov NCT03560687). Primary end-points were haemoglobin concentration on the day of hospital admittance and number of blood transfusions. Secondary end-points were haemoglobin drift, tolerance of treatment and cost-effectiveness of sucrosomial iron administration.**

**Results: Baseline haemoglobin in the treatment group was higher (by 0.67 g/dL; p<0.001) than that in the control group. The percentage of patients in the treatment group who required transfusion (35.4%) was half that in the control group (64.6%). The average number of transfused units per operation was 0.95 vs. 2.03 in the treatment and control groups, respectively. Haemoglobin drift was substantially similar in the two groups, and the tolerability of treatment was excellent (98%). The overall cost of treatment was 156 Euros less in the treatment group, expressed as a raw cost of transfusion.**

**Conclusion: In elective heart surgery, routine preoperative sucrosomial iron administration seems to be a safe, well-tolerated and cost-effective strategy to increase preoperative haemoglobin and reduce the need for allogeneic blood transfusions.**

## INTRODUCTION

Cardiac surgery is associated with substantial perioperative blood loss and a high risk of blood transfusions. Anaemia is frequently observed in patients scheduled for elective cardiac surgery. These conditions are associated with a substantial number of red blood cell (RBC) transfusions, adverse clinical outcomes, including mortality, and a prolonged hospital stay.[1-5]

Patient blood management (PBM) is a multimodal and multidisciplinary approach, based on the timely application of medical and surgical concepts designed to stimulate erythropoiesis, optimise haemostasis and minimise blood loss to improve the outcome of patients at risk.[6] In addition, PBM also results in improved use of transfusions and reduced healthcare costs.[7,8]

Previous studies have shown a high prevalence of iron deficiency (ID), independent of the presence of anaemia, among cardiac surgery patients,[9,10] who received more perioperative RBC transfusions than patients without ID.[11] In addition, preoperative ID, defined as ferritin <100 ng/mL, was independently associated with increased mortality, morbidity, and a prolonged hospital stay after cardiac surgery.[12]

Since iron plays a crucial role, not only in erythropoiesis, but also in many processes involved in energy production and efficient organ function,[13,14] there is a growing consensus regarding the treatment of preoperative ID even if it is not yet associated with anaemia.[14,15] This is particularly relevant in patients with depressed left ventricular function in whom treatment of iron deficiency has been shown to improve functional status within 4 weeks and to reduce both the need for hospital admission and even mortality.[16,17]

Moreover, patients undergoing uncomplicated heart surgery show a systematic reduction in haemoglobin between post-operative days 2 and 3, without active bleeding and with neutral fluid balance, known as haemoglobin drift, which, while commonly seen in many other surgical procedures,[18] is not yet fully understood.

Sucrosomial iron (SI) is a patented oral iron-delivery technology that may be considered even when iron deficiency is caused by concomitant inflammatory conditions (Fig. 1).[19,20]

The aim of the present study was to evaluate whether a 30-day course of oral SI supplementation before cardiac surgery could be helpful to improve patients' haemoglobin level and iron status and reduce blood transfusion requirements.

## MATERIALS AND METHODS

The trial protocol was approved by the local ethics committee (EH2018-003) and the study was registered at ClincalTrials.gov (NCT03560687) starting in November 2018, with randomization tables prepared ahead of the study.

Inclusion criteria were non-emergent surgery planning and age over 18y and under 90y. Exclusion criteria were emergent indication, baseline haemoglobin over 15.5 g/dL, or any diagnosed haematological disease. Patients who fulfilled the inclusion criteria and showed no exclusion criteria gave their informed consent to enter the study (Fig. 2).

Patients in the treatment arm received a daily administration of 60 mg SI (Cardiosideral®, PharmaNutra, Pisa, Italy; 2 capsules per day; each capsule contains30 mg of elemental iron, 80 mg of ascorbic acid, 2.5 µg of vitamin B12, and 150 µg of folic acid) starting 30 days before surgery. The comparator arm was labelled as the control and no specific intervention was added to routine preparation, to replicate the usual preoperative practice for the studied population. Patients undergoing scheduled surgery within a time-frame of less than 30 days from indication automatically were placed in the control arm.

Haemoglobin, ferritin, and serum iron were determined at the core laboratory of the facility, archived in the electronic patient data files, and then extracted for further calculations. The laboratory was blinded to the protocol, as were the physicians and caregivers.

Outcome measures were haemoglobin (main outcome variable), ferritin, and transferrin the day before surgery, postoperative haemoglobin drift, compliance with drug administration in the 30 days before surgery (%), number of allogeneic packed red blood cell units transfused, and cost-effectiveness in terms of

the cost of drug versus the savings from spared red blood cell units.

Haemoglobin drift was defined as the reduction in haemoglobin between postoperative days 2 and 4 in the absence of active bleeding (either chest tubes removed or drainage volume inferior or equal to 10 ml per hour) and with a neutral fluid balance.

The standard hospital transfusion protocol was applied in both groups, with a haemoglobin threshold of 7.0 g/dl in the absence of signs of oxygen-delivery failure.

## STATISTICAL ANALYSIS

The sample size calculation was based on the difference in the haemoglobin level from the day of hospital admittance. The superiority margin was set at 0.5 g/dl. A two-sided significance level of 5% was used and the power was set to 80%. Based on these assumptions, a total of 400 patients per arm were needed to test superiority. Thus, an enrolment of 1000 patients was projected to ensure that the findings would be robust.

Continuous data are expressed as mean and standard deviation or median and interquartile range after assessment of the normality of the distribution using the Kolmogorov-Smirnov test. Categorical data are presented as absolute values and percentages. Differences among variables in the two cohorts were assessed with an unpaired Student's t-test or Kruskal-Wallis test for continuous variables, and with a Chi-square test or Fisher's exact test for categorical variables, as appropriate. Differences among continuous variables at different time points were assessed by a paired Student's t-test with the Bonferroni correction and Friedman test.

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

SPSS (version 21, IBM Corp., Armonk, NY) and Excel 2016 (Microsoft, Redmond, WA) software were used for data analysis.

## RESULTS

From October 2018 to April 2020, 1084 patients were screened: 61 had exclusion criteria while 1023 fulfilled the inclusion criteria and were randomly assigned to one of the two study arms according to the rules stated in the Methods section. Of the hospitalized patients, 23 (11 in the treatment group and 12 in the control group) did not proceed to an operation (13 due to a diagnosis of active infective disease, 4 due to precedent unknown malignant oncologic disease, 4 due to urological problems that needed to be addressed before elective cardiac surgery, and 2 due to active gastrointestinal bleeding) and therefore were excluded from the study. Overall, 1000 patients were included in the analysis and their baseline characteristics are summarized in Table I.

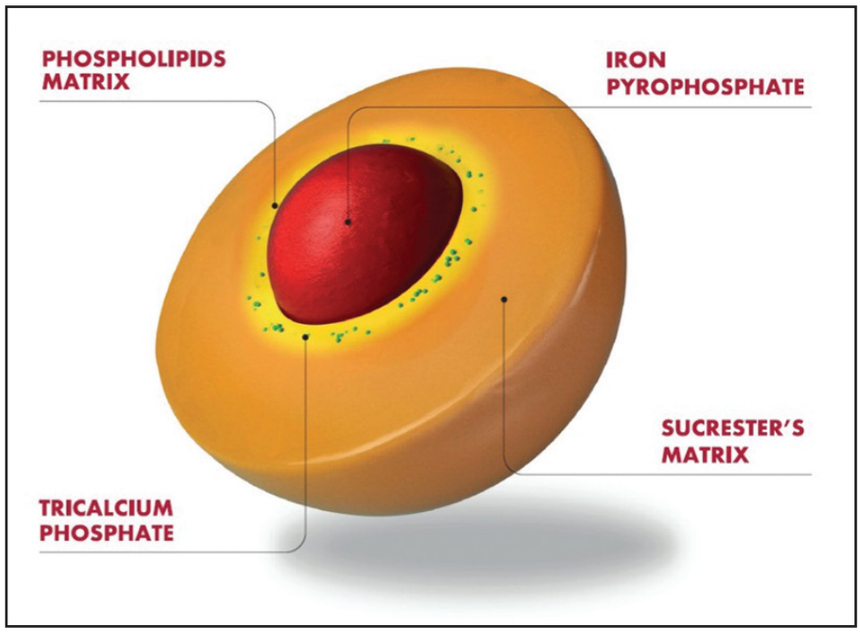


**Figure 1. Sucrosomial iron structure.**

The haemoglobin concentration at hospital admission in the treatment group (13.93 g/dl) was significantly greater than that in the control group (13.28 g/dl) ($p=0.001$) (Fig. 3). The serum ferritin concentration (184 vs 160 ng/mL) and serum iron (77 vs 73 µg/dL) also tended to be higher in the treatment group, but this difference was not statistically significant.

After the operation, the haemoglobin concentrations in the treatment group were again significantly greater than those in the control group (10.29 g/dl vs. 9.86 g/dl, respectively, on postoperative day 2, $p<0.001$; 9.64 g/dl vs. 9.28 g/dl, respectively, on postoperative day 4, $p<0.01$); postoperative blood loss was slightly higher in the control group (414 ml vs 354 ml). Despite these significant differences in absolute terms, the percentage reduction (haemoglobin drift) was not significantly different between the two groups (- 6.3% versus -5.9% p 0.23) (Table II).

Overall, 478 red blood cell units were transfused to 177 (35.4%) patients in the treatment group, and 1014 units were given to 323 (64.6%) patients in the control group (transfusion index: 0.95 units/ transfused patient vs. 2.03 units/transfused patient, respectively; $p=0.001$) (Figs. 4,5) This represents roughly a 50% reduction in total transfusion requirements, and also reflects that fewer patients in the treatment group (19.4%) required two or more red blood cell units compared to the control group (35.4%). Given average acquisition costs of € 200 per packed RBC unit and € 60 for the 30-day course of SI, preoperative iron supplementation resulted in a net savings of roughly € 156/patient (Table III).[8,21] These costs were calculated considering the reimbursement tariff in Italy for blood component acquisition between both private and public institutions and doesn't reflect the actual costs of red cell transfusion, since these tariffs reflect only the raw costs of materials used for blood collection, production, biologic qualification and pre-transfusion tests. In fact, the putative costs of red cell transfusion support in Europe may be significantly higher; an average weighted cost of 877.69 Euros for 2 units has been reported.[21]

Regarding iron parameters on the day before surgery, slight differences were

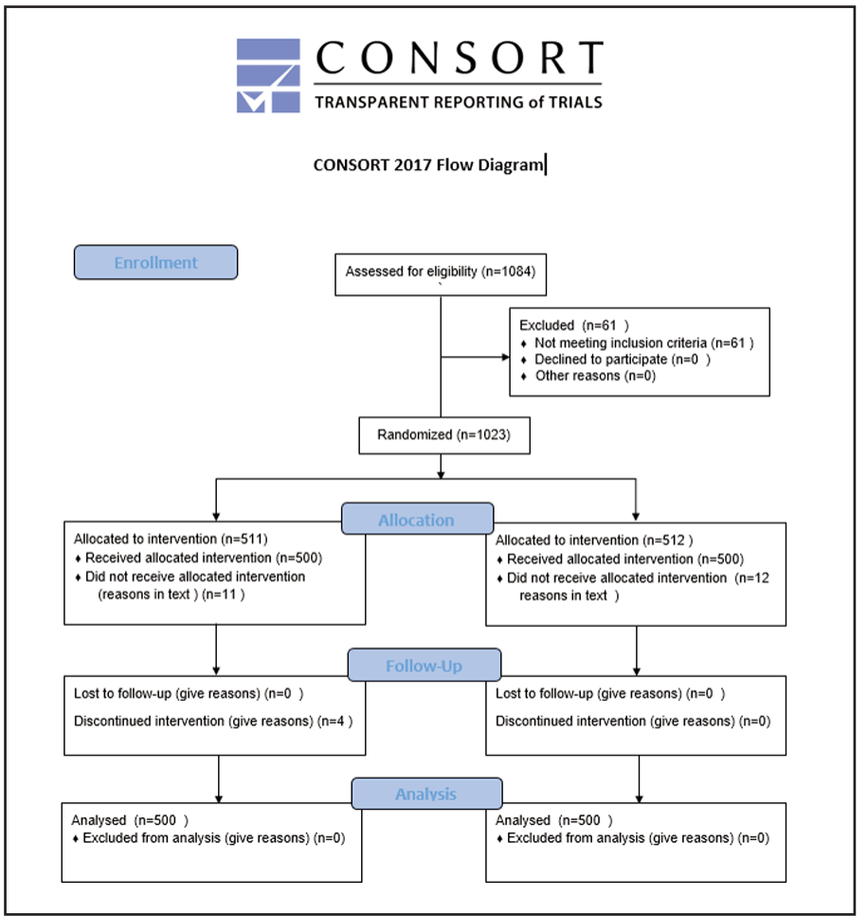


**Figure 2. Flow chart for patient distribution.**

observed in serum ferritin (+ 24 ng/mL) and serum iron (+4%) in the treatment group with respect to controls, but these differences were not statistically significant.

Most (98.2%) of the patients in the treatment group tolerated the 30-day preoperative course of SI; iron supplementation was reduced to a single daily capsule (30 mg) in 5 participants (1%), and interrupted in 4 (0.8%) due to gastrointestinal side-effects (Fig. 6). No between-group differences in postoperative complication rates, postoperative intensive care unit or hospital length of stay, or 30-day mortality rates were observed (Table I).

## DISCUSSION

ID, with or without anaemia, is frequently observed in patients undergoing cardiac surgery.[1,2] Several retrospective studies have documented an association between ID, with or without anaemia, and increased RBC transfusions and adverse clinical outcomes (such as increased length of hospital stay, acute kidney injury, and mortality).[1,2,5,11]

In a recent large prospective randomized trial comparing the application of a liberal versus a restrictive RBC transfusion trigger, a similar difference in median RBC transfusions of 1 unit was found without differences in clinical secondary outcomes.[22] Different clinical outcomes are observed in cardiac surgery patients with low haematocrit values (<25%) who received RBC transfusions: those who were exposed to RBC transfusion had an increased cardiac and renal morbidity and increased hospital mortality.[23] Since the preoperative haemoglobin concentration is a strong predictor of the need for perioperative transfusion, preoperative anaemia should be treated as early as possible before major surgery. This could be accomplished in an outpatient setting allowing a more timely and complete restoration of the RBC mass, which might lead to a greater reduction of RBC transfusions and, eventually, to improved clinical outcomes.

Preoperative correction of iron deficiency and anaemia is an integral part of the concept of PBM and is recommended by major professional societies of cardiothoracic surgeons and anaesthesiologists.[24,25] Although the success of this concept has been demonstrated in a large general surgical patient population of more than 605,000 patients,[7,8] its benefit in cardiac surgery has so far only been shown in relatively small cohorts.[26] The results of this study highlight that the preoperative correction of anaemia and iron deficiency might result in a reduction of allogeneic RBC transfusions in patients undergoing cardiac surgery, which makes it an essential pillar of PBM. These results become even more relevant considering that diagnosis of preoperative anaemia and resulting implementation of appropriate treatment are not part of standard care in cardiac surgery in many institutions, including our clinical practice. Therefore, these patients would have had surgery without any pre-operative optimization of haemoglobin and iron status.

Data from the United Kingdom show that more than 30% of all patients undergoing cardiac surgery are anaemic preoperatively.[2] Similar data were published for Spain, and functional ID was observed in almost 50% of the patients.[10] In chronic inflammation, which is frequently observed in atherosclerotic patients, hepcidin decreases iron absorption and prevents iron recycling, resulting in an iron-restricted erythropoiesis, despite normal iron stores (functional iron deficiency). Patients with atherosclerosis who are undergoing CABG surgery are in a low-grade inflammatory state,[14,27,28] which increases ferritin regardless of the iron status. For these patient populations, iron deficiency should be considered to be present if serum ferritin is <100 ng/mL or reticulocyte haemoglobin is <27 pg.[9]

Conventional oral iron salts have been shown to be ineffective for treating ID in the context of inflammation and in patients with heart failure, and the use of intravenous iron is recommended in these situations.[9,29] However, relatively few studies have addressed the use of parenteral iron alone for treating preoperative anaemia in cardiac surgery.[30-32] These trials were relatively small and varied with respect to the formulation, dosing, and timing of intravenous iron therapy. In general, perioperative intravenous iron resulted in an increase in haemoglobin, but had little or no effect

**Table I**
**Patient demographic and clinical characteristics**

| | Intervention group N = 500 | Control group N = 500 | p |
|---|---|---|---|
| Age (years) | 65.9 (19-87) ± 12.1 | 69.2 (24-86) ± 10.0 | 0.001 |
| Male gender, n (%) | 321 (64%) | 304 (61%) | 0.26 |
| Height (cm) | 170 (143-197) ± 9.0 | 168 (145-199) ± 9.4 | 0.002 |
| Weight (kg) | 75.9 (40-140) ± 12 | 75.1 (40-120) ± 14.2 | 0.37 |
| Family history of cardiovascular disease, n (%) | 194 (39) | 183 (37) | 0.51 |
| Diabetes, n (%) | 154 (31) | 159 (32) | 0.68 |
| Hypercholesterolaemia, n (%) | 300 (60) | 295 (59) | 0.74 |
| Smoking history, n (%) | 183 (37) | 179 (36) | 0.79 |
| Hypertension, n (%) | 390 (78) | 374 (75) | 0.23 |
| Severe renal impairment, n (%) | 9 (2) | 12 (2.4) | 0.66 |
| Unstable angina, n (%) | 70 (14) | 65 (13) | 0.73 |
| Ejection fraction (%) | 53 (24-75) ± 7 | 51 (28-75) ± 8 | 0.001 |
| Recent myocardial infarction, n (%) | 20 (4) | 23 (5) | 0.53 |
| Severe pulmonary hypertension, n (%) | 14 (2.8) | 12 (2.4) | 0.69 |
| Postinfarct septal rupture, n (%) | 0 (0) | 0 (0) | n.a. |
| Isolated valve replacement, n (%) | 246 (49.4) | 251 (50.6) | 0.70 |
| Isolated coronary artery bypass grafting, n (%) | 82 (16.4) | 87 (17.4) | 0.67 |
| Combined procedure, n (%) | 172 (34.4) | 161 (32) | 0.46 |
| ICU lenght of stay (days) | 2.6 (1-91) ± 5.4 | 3.2 (0-54) ± 4.7 | 0.06 |
| Postoperative hospital length of stay (days) | 13.3 (1-99) ± 8.4 | 15.2 (1-280) ± 15.7 | 0.02 |
| PostOP 30-day survival, n (%) | 492 (98.4) | 483 (96.6) | 0.07 |

Data are presented as mean (minimum - maximum) ± Standard Deviation or number (percentage); ICU, intensive care unit; PostOP, postoperative; P, intervention group vs. control group.

on red blood cell transfusion.

In contrast to current evidence of poor adherence to treatment with traditional oral iron salts, mostly due to gastrointestinal side effects, our study shows that SI is very well-tolerated. Indeed, in only 9 of the 500 patients, the SI dose was reduced to a single daily capsule or suspended completely due to gastrointestinal side effects, whereas 491 (98.2%) completed the treatment course uneventfully. In line with previously published observations, these data demonstrate the excellent gastrointestinal tolerability of SI and differentiate it from all other oral iron products available commercially.[20]

Regarding the efficacy on the day before surgery, significantly higher haemoglobin (+0.65 g/dl), ferritin (+25 ng/ml) and iron serum (+4%) were observed in the treatment group compared to the control group .

This increase in preoperative haemoglobin is similar to that reported by Klein et al.[32] for the administration of preoperative intravenous iron (+0.84 g/dl). The improvements in the haemoglobin concentration might enable higher oxygen delivery and use over the entire perioperative period, and could potentially impact not only blood transfusions but also clinical outcomes in general. However, how to best document functional improvements is still a matter of debate. While the 6-minute walking test is sometimes used for this evaluation, unfortunately, severe pulmonary or kidney impairment, as well as reduced mobility, are all major confounding factors that make this test unreliable in our setting.[33]

A recent meta-analysis of randomized controlled trials and observational studies investigated the effect of preoperative IV iron therapy, compared with oral iron

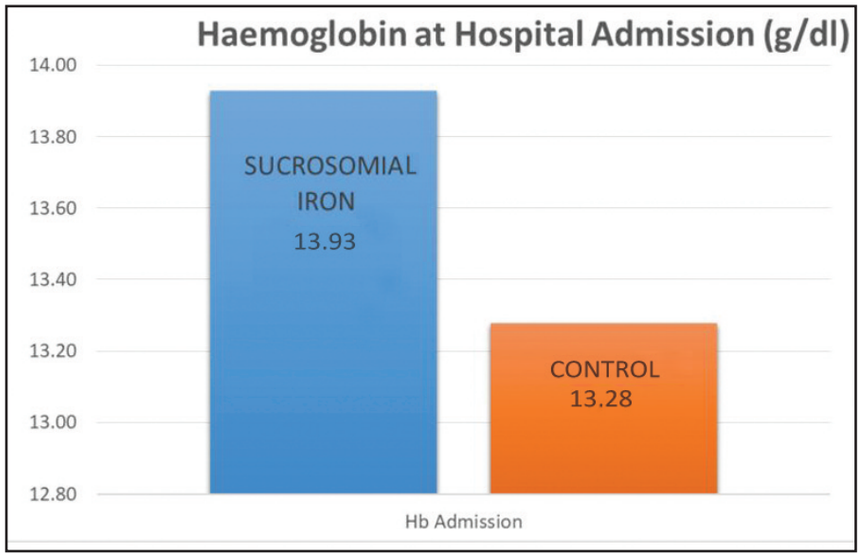


**Figure 3. Haemoglobin levels at hospital admission**

**Table II**
**Perioperative changes in haemoglobin and iron parameters**

| | Intervention group N = 500 | Control group N = 500 | p |
|---|---|---|---|
| Hospital admission haemoglobin (g/dl) | 13.93 (8.9-18.0) ± 1.54 | 69.2 (24-86)13.26 (6.9-17.1) ± 1.73 | 0.001 |
| Haemoglobin on postoperative day 0 (g/dl) | 12.42 (7.3-17.1) ± 1.45 | 11.99 (7.7-16.3) ± 1.51 | 0.001 |
| Haemoglobin on postoperative day 2 (g/dl) | 10.29 (7.0-14.0) ± 1.33 | 9.86 (6.7-13.3) ± 1.16 | 0.001 |
| Haemoglobin on postoperative day 4 (g/dl) | 9.64 (6.2-14.7) ± 1.32 | 9.28 (6.5-12.9) ± 1.18 | 0.001 |
| Haemoglobin drift (%) | 6.3 | 5.9 | 0.23 |
| Serum iron at hospital admission (%) | 76.4 (14-282) ± 29.8 | 73.4 (2-552) ± 48.1 | 0.26 |
| Serum ferritin at hospital admission (%) | 184.32 (5-2151) ± 233 | 160.24 (6-960) ± 150 | 0.11 |

Data are presented as mean (minimum - maximum) ± Standard Deviation; P, intervention group vs. control group; *P<0.01, preoperative vs. baseline

or no iron therapy, on postoperative outcomes in patients undergoing cardiac surgery with preoperative anaemia.[34] IV iron was associated with fewer units transfused per patient compared to the use of no iron, with a mean difference of 1.22 red cell units. This evidence supports the use of intravenous iron as an effective treatment and, at least in absolute terms, this may seem to be a greater cost savings than that found in the present study. However, the direct and indirect costs of IV iron infusion must also be considered,[34] along with the fact that, as opposed to simple, low-cost at-home supplementation with SI, the safe and timely use of intravenous iron is challenging in terms of clinical and logistic support. This confirms that pre-operative iron administration in heart surgery is a useful, cost-effective strategy and should be considered as part of the standard of care.

In this regard, the present results suggest that oral SI administration is a promising supplementation choice. In fact, SI has also been used in PBM programs for orthopaedic surgery, where it has been shown to improve preoperative iron status in elderly patients[35] and to limit the post-operative fall in the haemoglobin concentration, decrease RBC transfusion, and shorten the length of hospital stay, thus reducing costs.[36] This study involved a large sample of patients who underwent elective heart surgery at a single institution within a relatively short period. This ensures uniformity in surgical and anaesthetic techniques, surgeon expertise and perioperative care, thus contributing to the robustness of the data.

However, some potential limitations should also be acknowledged. First, because of this study's single-centre design, the results may not be extrapolable to other centres (masked selection connected to the referral of patients, expertise of the centre, distribution of the population study, quality of anaesthesiology support, etc.). Therefore, the results need an independent external

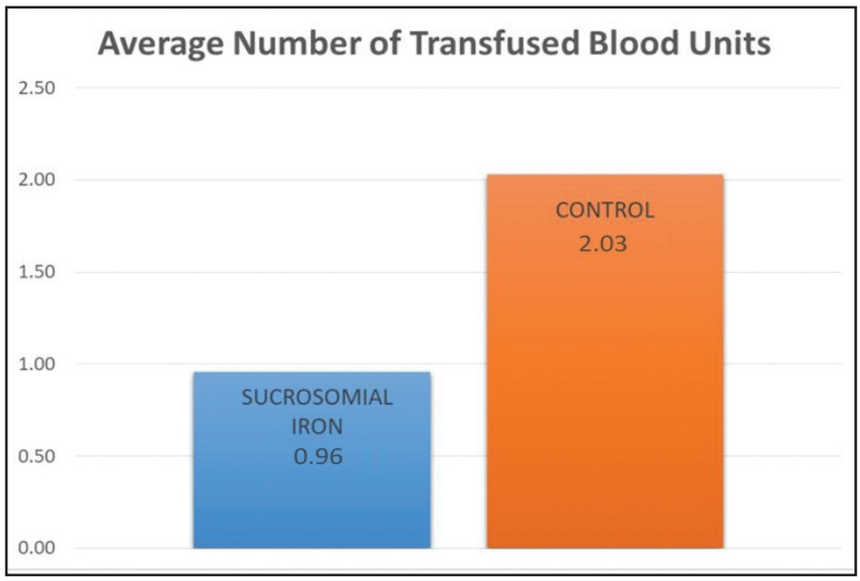


**Figure 4. Average number of transfused units.**

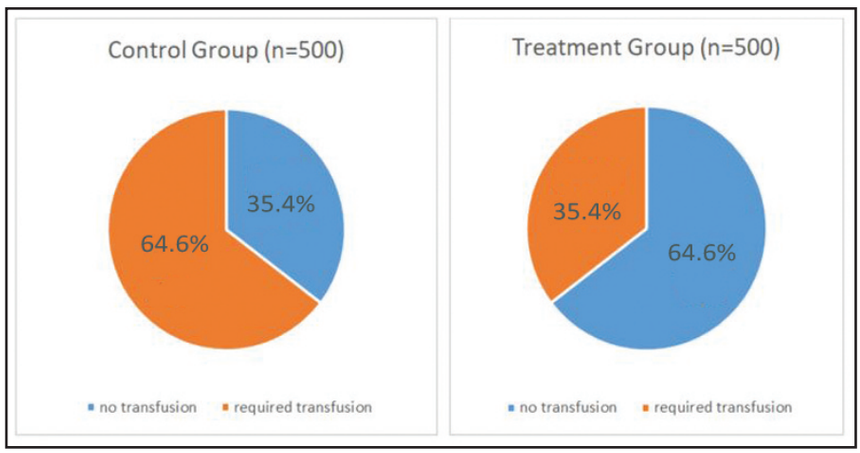


**Figure 5. Ratio of patients receving any amount of transfusion to patients who were not transfused**

**Table III**
**Blood loss, red blood cell transfusion and costs**

| | Intervention group N = 500 | Control group N = 500 | p |
|---|---|---|---|
| Bleeding at 12 hours after chest closure (ml) | 354 (64-2120) ± 271 | 414 (80-3300) ± 360 | 0.005 |
| Transfused patients | 177 (35.4) | 323 (64.6) | 0.001 |
| Transfused red blood cells (units) | 478 | 1014 | 0.001 |
| Overall red blood cell transfusion index (units/patient) | 0.95 (0-30) | 2.03 (0-58) | 0.001 |
| Transfused patients receiving 2 or more units (%) | 19.4% | 35.4% | 0.001 |
| Cost of blood transfusion (€/patient) | 190 (0-6000) | 406 (0-11600) | 0.001 |
| Cost of iron supplementation (€/patient) | 60 | 0 | 0.001 |
| Total cost per patient (€) | 250 | 406 | 0.001 |

Data are presented as mean (minimum - maximum) ± Standard Deviation; P, intervention group vs. control group.

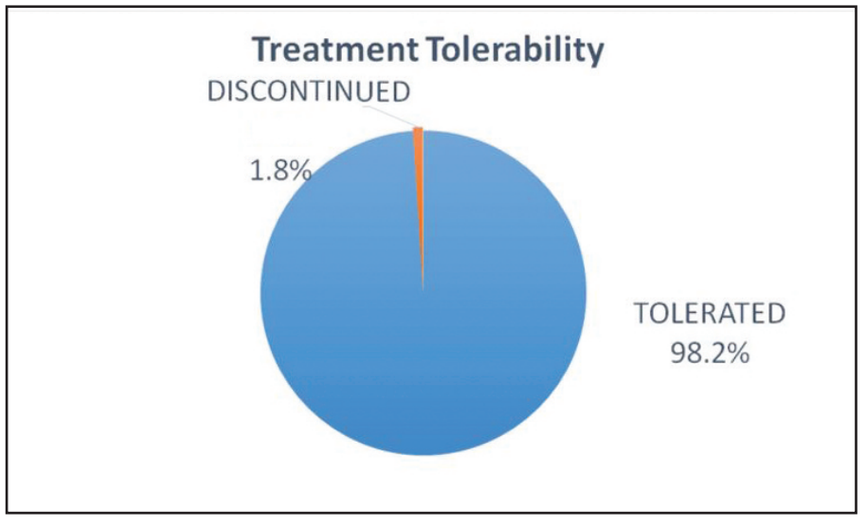


**Figure 6. Percentage of rejection of therapy due to intolerance.**

confirmation.

Second, we evaluated mainly haematological and transfusion parameters, but not functional parameters, such as with the 6-minute walking test, which means that we cannot draw any conclusions regarding any potential improvement in the patient's functional status. This should be addressed in a future, properly designed study.

Third, a proper comparison of pre-randomization iron parameters could have been useful to establish if the one-month timeframe was adequate. However, only a fraction of the patients had reliable data on this point and therefore such an analysis could not be performed.

In conclusion, preoperative SI administration seems to be a safe, well-tolerated and cost-effective method for increasing preoperative haemoglobin and decreasing transfusion requirements in elective heart surgery. Therefore, when the time-frame allows for a 30-day course of preoperative treatment, the proposed iron supplementation protocol may be a valuable strategy for this patient population. STI

## AUTHORS' DISCLOSURES

The authors declare that there are no conflicts of interest.

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