Impact of a bundle of care (intravenous iron, erythropoietin and transfusion metabolic adjustment) on post-operative transfusion incidence in cardiac surgery: a single-centre, randomised, open-label, parallel-group controlled pilot trial

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Summary

Background Red blood cell (RBC) transfusions are frequent in patients after cardiac surgery. This study assessed whether a bundle of care including pre-operative and post-operative administration of erythropoietin (EPO) with intravenous iron supplementation, and restrictive transfusion adjusted for $ScvO_2$ could result in reduced postoperative transfusions.

Methods In this single-centre, randomised, open-label, parallel-group controlled pilot study, patients undergoing elective cardiac surgery with high risk of transfusion in a University Hospital were enrolled by the investigator and the randomisation procedure using a central internet-based system was made by the clinical research assistant. Since the trial was open-label, no masking was used. Patients were assigned (1:1) to either the STOP group (40,000 IU subcutaneous EPO combined with 20 mg/kg intravenous ferric carboxymaltose if Hb < 13 g/dL the day before surgery or at ICU admission, and RBC transfusion if Hb ≤ 8 g/dL and $ScvO_2$ ≤ 65%, or additional EPO dose if 8 < Hb < 13 g/dL) or to the control group (RBC transfusion if Hb ≤ 8 g/dL, or, if 8 < Hb < 13 g/dL, intravenous iron sucrose 200 mg or 300 mg according to weight). Primary outcome was the incidence of postoperative RBC transfusion up to hospital discharge or postoperative day 28. The trial is registered with ClinicalTrials.gov, NCT04141631.

Findings Between Jan 20, 2020, and Sept 6, 2022, among 128 patients enrolled, 123 (male, 54.4%, 67/123) were included in the full analysis set: 62 in the STOP group and 61 in the control group. Nine patients (14.5%, 9/62) in the STOP group required RBC transfusion vs 19 (31.2%, 19/61) in the control group (odds ratio 0.37 [95% CI: 0.15–0.91], p = 0.03). The median length of follow up to transfusion was 2.6 days (1.5; 4.6) and 3.3 (1.6; 4.2) in control and STOP groups respectively (p = 0.61).

Interpretation The bundle of care may reduce postoperative RBC transfusion. The findings should be taken with caution due to the unblinded and exploratory nature of the study.

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Keywords: Cardiac surgery; Anaemia; Transfusion; Patient blood management; Iron supplementation; Erythropoietin

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Research in context

Evidence before this study
Following a literature search conducted up to December 1st 2023, we identified published papers in English language from academic databases, mainly MEDLINE, through PubMed search using keywords such as "Anaemia", "Cardiac surgery", "Patient Blood Management", "Erythropoietin", "Iron supplementation", "Red blood cell transfusion" and their combinations. Anaemia exposes patients to postoperative red blood cell (RBC) transfusion, and both are recognized as strong independent predictors of morbidity and mortality. Perioperative anaemia optimization and transfusion avoidance are therefore key issues of Patient Blood Management (PBM) programs. Several approaches to improve transfusion sparing have been previously investigated separately in cardiac surgery. Ultrashort preoperative erythropoietin (EPO) administration combined with iron supplementation, has shown quite good efficacy to reduce postoperative RBC transfusion in 3 prospective randomized controlled trials (RBC transfusion exposure decreases of 15–40%). ScvO2, a metabolic marker to estimate anaemia tolerance, has been used to individualize RBC transfusion beyond haemoglobin concentration threshold in 2 randomized trials, which showed a significant reduction of transfusion exposure (RBC transfusion exposure decreases of 21–32%). However, no study has addressed the effect of a bundle of these procedures yet.

Added value of this study
This prospective, randomized study investigated in cardiac surgery patients at high risk of perioperative transfusion, the impact of a bundle of PBM care, which included, beside a restrictive transfusion strategy based on haemoglobin threshold at 8 g/dL, ultrashort preoperative EPO combined with iron supplementation, ScvO2 to adjust postoperative RBC transfusion, and, eventually, postoperative EPO combined with iron supplementation to treat postoperative anaemia. The results show that the bundle of care induced a substantial reduction of postoperative RBC transfusion (50%), as well as a lower incidence of postoperative anaemia, when compared to standard care with a restrictive transfusion strategy and iron supplementation.

Implications of all the available evidence
Improvement of PBM programs is a continuous challenge. In previous studies, EPO and iron supplementation, and SvcO2 had shown good independent potential to reduce anaemia and to spare RBC transfusion even during restrictive strategy. As demonstrated in the present study, combination of these approaches, added to postoperative EPO eventually, seems even more effective as a bundle of care to reduce transfusion and to prevent long-term anaemia.

Introduction

Pre-operative anaemia has an increasing prevalence due to an ageing population suffering from more chronic diseases and affects up to 20–40% of patients who are scheduled for cardiac surgery.[1,2] Pre-operative anaemia is an independent factor of adverse outcome on its own and favours peri-operative allogenic red blood cell (RBC) transfusion which is also a predictor of worst outcome[3]; as a matter of fact, anaemia and transfusion have a cumulative negative impact on post-operative mortality.[4,5] Blood conservation in cardiac surgery is aimed at reducing both risks. Therefore, patient blood management (PBM) strategy has been encouraged to prevent anaemia and transfusion-induced morbidity and mortality.[6,7]

To address the issue of pre-operative anaemia (besides investigating its aetiology and related treatments), iron supplementation and recombinant human erythropoietin (EPO) have been proposed to optimise production of the patient's own haemoglobin (Hb) (haematopoiesis).[8,9] Intravenous iron has demonstrated good efficacy, with a single dose of 1 g of intravenous iron as ferric carboxymaltose (FCM) providing enhanced Hb concentration increase and better tolerance than oral iron supplementation.[10,11] Similarly, EPO has also been suggested in cardiac surgery with promising results.[11,12]

Optimising haematopoiesis with the use of iron supplementation and EPO to reduce pre-operative anaemia has therefore become an integral part of the PBM guidelines.[6,7]

Restrictive blood transfusion is another strong recommendation although its benefits on post-operative outcome are still confusing since no superiority has been exhibited compared to liberal transfusion on post-operative mortality.[13,14] The absence of a definite advantage of adopting a restrictive strategy may be related to flaws in its initial conception based on a fixed, low Hb threshold for all patients. Venous oxygen saturation (SvO2), which provides an interesting link between Hb concentration and tissue oxygen delivery, may serve as an objective marker of anaemia tolerance. Two recently published RCT, which used central SvO2 (ScvO2) in anaemic patients to adjust RBC transfusion decision with a rather liberal transfusion strategy (transfusion threshold 9 g/dL), showed a significant decrease in transfusion incidence, meaning transfusion was avoided in some patients who would otherwise have received transfusion if Hb concentration alone had been considered.[15,16] Whatever the outcome, restrictive transfusion strategy may result in persistent post-operative anaemia.[13,14] Whether combining restrictive transfusion adjusted with ScvO2 to avoid unnecessary

transfusion and use proactive treatment with iron supplementation and EPO to prevent post-operative anaemia may reduce transfusion and improve outcomes is still an unresolved issue.

In this pilot study, we aimed to evaluate a bundle of care, which included peri-operative administration of EPO and FCM associated with restrictive transfusion strategy adjusted for $ScvO_2$, on postoperative blood savings and anaemia in cardiac surgery patients at higher risk of transfusion.

Methods

Study design

This was a single-centre, randomised, open-label, parallel-group controlled pilot trial conducted at the Anaesthesiology and Intensive Care Department of the Montpellier University Hospital (Montpellier, France). This trial protocol was approved by the local Ethics Committee (Sud Mediterrannée V 19.04.02.61948) and the French National Agency for the Safety of Medicines and Health Products (ANSM) and has been registered online on the ClinicalTrials.gov website (NCT04141631). An independent trial safety committee monitored trial benefit/risk ratio and safety for the entire duration of the study. After the commencement of the trial, a change in inclusion criteria (amendment to the definition of anaemia) was decided upon to increase the number of patients treated by the bundle of care (see below *Procedures* section). The change was agreed by the local Ethics Committee on 15 July 2020.

Participants

Patients aged 18 or older scheduled for elective on-pump cardiac surgery with high risk of transfusion defined by a TRUST score ≥3[17] were eligible for enrolment (Table S1, Appendix p2). Patients previously treated with EPO were excluded. All patients signed a written informed consent. Detailed inclusion and exclusion criteria are provided in the Appendix (Table S2, Appendix p3).

Randomisation and masking

Participants were enrolled only if they fulfilled the inclusion criteria. If the patient was eligible, after consent, he (she) was enrolled by the investigator and the randomisation procedure was made by the clinical research assistant (CRA). Patients were randomly assigned to the study groups (Control and STOP) before surgery. Randomisation was performed with a 1:1 allocation ratio, stratified on gender and BMI (<25 kg/m^2, [25–30] kg/m^2, ≥30 kg/m^2) using a minimisation process and carried out using a central internet-based randomisation system (Capture System Software, Ennov Clinical, randomisation module), which was configured by the data manager.

Since the trial was open-label, no masking was used. The randomisation software was exclusively managed by the clinical research assistant (CRA) to minimize the potential for predictability in group assignment. Access to the complete database was restricted to the CRA and the data manager, ensuring confidentiality to reduce the risk of bias. The investigators have access to the eCRF of their patients to validate the clinical data entered by the CRA. The analyst drafted the Statistical Analysis Plan (SAP) after the end of the study (final version approved on 29 March 2023).

Procedures

Anaemia was initially defined as Hb concentration <12 g/dL and changed after local Ethic Committee and ANSM approvals to <13 g/dL, which matches the definition in the international consensus statement on the peri-operative management of anaemia and iron deficiency.[18] Iron deficiency was defined as ferritin plasma concentration <100 μg/L or transferrin saturation coefficient (TSC) < 20%.[19,20]

For all included patients, peri-operative management was standardised. Specifically, according to our institutional PBM protocol: 1- heparin and protamine were monitored by activated clotting time (Hepcon HMS®, Medtronic, Minneapolis, MN); 2- tranexamic acid was administered during cardiopulmonary bypass (CPB); 3- a point of care (POC) coagulation algorithm (TEG®, Haemonectics, Braintree, Massachusetts, MA) was used to manage blood products and coagulation drugs; 4- RBC units were transfused to maintain Hb concentration >7 g/dL during CPB.

Hb was measured routinely (i) before surgery, (ii) during CPB, (iii) at arrival in the ICU, (iv) every 12 h during the first two days after surgery, then (v) once daily in the ICU, (vi) once a week and at the clinician's discretion in the surgery ward, (vii) after any transfusions as well as (viii) within the three months after hospital discharge. Ferritin plasma concentration and TSC were measured before surgery, on the first post-operative day (POD 1) and at hospital discharge (or POD 28).

In the control group, post-operative anaemia was treated in accordance with our PBM protocol: one RBC unit was transfused whenever Hb concentration was ≤8 g/dL. If Hb was >8 g/dL, 200 mg or 300 mg (as per weight, < or >70 kg respectively, maximal dose of 15 mg/kg) iron sucrose (Venofer®, Vifor AG, St Gallen, Switzerland) was administered intravenously with two injections at 24-h intervals (Study design, Figure S1, Appendix p8).

In the STOP group, pre-operative anaemia was treated by intravenous administration of 20 mg/kg (maximum of 1000 mg) FCM (Ferinject®, Vifor AG, St Gallen, Switzerland) associated with subcutaneous EPO α at 600 IU/kg (maximum 40,000 U) (Binocrit®, Sandoz GmbH, Kundl, Austria) the day before surgery. In

the ICU, post-operative transfusion was adjusted for $ScvO_2$ measured in a blood sample withdrawn from the distal lumen of the central venous catheter by oximetry with POC blood gas analysis in the ICU (Gem 4000, Premier Instrumentation Laboratory Werfen Company, Bedford, Massachusetts, USA). More specifically, if Hb was ≤8 g/dL and $ScvO_2$ ≤ 65%, one RBC unit was administered. Transfusion was repeated whenever Hb concentration was ≤8 g/dL and $ScvO_2$ ≤ 65%. In case of $ScvO_2$ > 65% and Hb < 7 g/dL, RBC transfusion was carried out. If $ScvO_2$ > 65% and Hb ≤ 8 g/dL, no RBC transfusion was provided but EPO and FCM could be administered if not given within the seven previous days (Study design, Figure S1, Appendix p8).

Clinicians were permitted to deviate from the Hb/$ScvO_2$ criterion when deciding whether to transfuse in the case of critical clinical conditions including (i) severe sepsis, (ii) septic shock, (iii) haemodynamic instability (defined either by massive bleeding, by the introduction of inotropic or vasopressor treatment or by a significant change in the dosage (increase or decrease of more than 20%) or (iv) an episode of severe pulmonary failure (defined by partial pressure of oxygen in the arterial blood on the fraction of inspired oxygen ratio <200).

From ICU exit up to hospital discharge or POD 28, anaemia was managed identically according to the PBM protocol in both groups, meaning that transfusion was considered when Hb was ≤8 g/dL with no further central $ScvO_2$ measurements in the STOP group. A second combined administration of EPO and FCM could be done in the Stop group by respecting a delay of seven days between two administrations.

Summary of the procedures is provided in the Supplementary Material (Figure S1, Appendix p8).

Outcomes

The primary endpoint was the proportion of patients transfused with RBC units after surgery, up to hospital discharge or POD 28 if their hospital stay exceeded 28 postoperative days (so called "study discharge").

Secondary endpoints were the number of patients transfused in the ICU, in the surgical ward, the total number of anaemia events with either RBC transfusion or anaemia treatment in the ICU or in the surgical ward, anaemia incidence at ICU admission, POD 1, ICU discharge, hospital discharge and within the first three months after hospital discharge and Hb concentration at study discharge and within the first three months after hospital discharge.

Other secondary outcomes included lengths of the ICU and hospital stays and post-operative complications at the time of study discharge: incidence of mortality, infection (respiratory, septicemia), ischaemic events (myocardial infarction, stroke, mesenteric ischaemia), thromboembolic event (pulmonary embolism), acute kidney injury according to KDIGO classification or liver dysfunction (if plasma hepatic enzymes or bilirubin exceeded the standard value 2-fold).

Transfusion costs including number of post-operative RBC units, EPO administration and iron supplementation were also determined for both groups at the time of study discharge.

Adverse events (AE) and serious adverse events (SAE) were collected from inclusion in the study-to-study discharge. The number of AE were described overall then by group using the number of subjects who had at least one AE and the associated percentage. The number of SAE were described in the same way. Accountability was checked and validated by the trial safety committee.

Statistical analysis

According to a previous study,[15] the incidence of transfusion after surgery is around 50% for patients whose Trust score is ≥ 3. Assuming that the incidence of transfusion would be 25% in the STOP group vs 50% in the control group, the number of subjects required was estimated at 58 patients per group taking a type I error rate of 5% and a power of 80% in the event of a bilateral alternative hypothesis. With a rate of lost to follow-up or unusable data of around 10%, a total of 128 patients were to be included.

All the analyses were performed according to the intention-to-treat principle using the full analysis set (FAS) defined as all randomised patients for whom the primary endpoint is available. A sensitivity analysis was conducted for the primary endpoint on the per-protocol set defined as all randomised patients included in the FAS without any major protocol deviations affecting the evaluation of treatment efficacy.

The primary endpoint was compared between the STOP and control groups using a logistic regression adjusted for stratification factors. Effect size was estimated using odds ratio (OR) together with its 95% confidence interval.

The proportion of patients transfused in the ICU, in the surgical ward, anaemia incidence and the occurrence of post-operative complications are reported as frequency and percentage and were compared between the two groups using logistic regression adjusted for stratification factors. The total number of red blood cells transfused in the ICU, at study discharge, length of the ICU and hospital stays and treatment costs were compared between groups using a Wilcoxon test. Mean (SD) and median (IQR) are reported for length of the ICU and hospital stays. Hb concentration was compared between the STOP and control groups using a linear mixed model for repeated measurements including Hb concentration values before surgery, operative nadir, at POD 1, at ICU admission, at ICU exit, at the time of study discharge and within the first 3 months after hospital discharge and was adjusted for stratification factors. The incidence of mortality was analysed using a Kaplan–Meier estimator and log-rank test.

Additional analyses included sub-group analysis on patients who did not undergo transfusion during surgery. The primary endpoint was compared between the STOP and control groups using a logistic regression adjusted for stratification factors. Effect size was estimated using OR together with its 95% confidence interval.

Statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, North Carolina, NC). p-value less than 0.05 was considered to indicate statistical significance. All reported p-values are two-sided and have not been adjusted for multiple testing, except for Hb concentration where a correction using the method stated by Benjamini Y et al. based on false discovery rate approach was applied.[21] Given the low number of missing data (3.9% for the primary outcome), no imputation was performed.

Role of funding sources

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Results

The enrollment started on 13 January 2020, and the last patient follow up ended on 15 June 2022. Between 20 January 2020 and 6 September 2022, 128 patients out of 149 patients eligible for enrolment underwent randomisation and 123 were finally included in the FAS: 62 in the STOP group and 61 in the control group respectively. In the per protocol (PP) set, 52 and 59 patients were included in the STOP and control groups respectively (Flow Chart, Fig. 1). Follow-up of Hb values in the first three months after hospital discharge was retrieved in 87 patients (71%). Baseline demographic, clinical and biological characteristics are reported in Table 1. The mean age was 70.1 ± 8.9, the mean TRUST score was 3.7 ± 0.7, mean pre-operative Hb value was 12.9 ± 1.3 g/dL and 56.1% of patients were female. Incidence of pre-operative anaemia was 48% (n = 30/62) and 57% (n = 35/61) in the STOP and control groups respectively. A total of 21.1% (n = 26) of patients received a blood product in the operating room.

From ICU admission to study discharge, 14.5% (n = 9) of patients in the STOP group required RBC transfusion vs 31.2% (n = 19) in the control group (p = 0.03). The median length of follow up to transfusion was 2.6 days (1.5; 4.6) and 3.3 (1.6; 4.2) in control and STOP groups, respectively (p = 0.61) (Kaplan Meyer representation of time with free RBC transfusion: Figure S2, Appendix p9). Exposure to RBC transfusion was less frequent in the STOP group vs the control group: OR 0.37 [95% CI: 0.15–0.91]. Sensitivity analysis on the PP population showed similar results (OR 0.24 [95% CI: 0.08–0.70], p = 0.01). Additional analyses were performed. First, on the primary endpoint adjusted to preoperative haemoglobin concentration, which gave similar results with an OR of 0.40 [95% CI: 0.16; 0.99], and 0.26 [95% CI: 0.08–0.78] on PP population. Second, considering only anemic patients (n = 65; STOP group: n = 30, Control group: n = 35) with an OR of 0.29 [95% CI 0.08; 1.0]. Sub-group analysis on patients not transfused during surgery, which concerned 100 patients, (47 and 53 in the STOP and the control groups respectively), exhibited a higher incidence of post-operative RBC transfusion in controls compared to STOP group patients: 14 (24.4%) vs 5 (10.6%) respectively (OR [95% CI]: 0.32 [0.10; 0.99], p = 0.047).

More specifically, there was a trend towards a greater number of transfused patients in the control group in the ICU and in the surgical ward than in the STOP group: 4.8% (n = 3) vs 14.8% (n = 9) and 12.9% (n = 8) vs 24.6% (n = 15), OR 0.29 [0.07–1.14], p = 0.08 and OR 0.44 [0.17–1.14], p = 0.09 respectively (Cumulative numbers of RBC at study discharge reported in Table S3, Appendix p4). Mean Hb value before transfusion was 7.5 ± 0.5 g/dL and 7.7 ± 0.8 g/dL for the control group and STOP group respectively.

In the STOP group, 40.3% (n = 25) of patients received their first EPO and FCM administration the day before surgery, 50% (n = 31) of patients at the time of ICU admission and 3% (n = 2) of patients in the surgical ward. It should be noted that five anaemic patients were not administered treatment the day before surgery because they were recruited before the study design modification although four were given the combined treatment at the time of ICU admission. RBC transfusion was performed for a mean $ScvO_2$ of 54.8 ± 7.5%; one out of six post-operative anaemia events (16.7%) was associated with a $ScvO_2$ > 65%. Finally, one patient was not transfused and did not receive EPO and FCM treatment during the study (Fig. 2).

In the control group, 60 patients (98.4%) were administered iron sucrose at the time of ICU admission (Fig. 2). More anaemia events were treated with RBC transfusion in the control group than in the STOP group (mean number of RBC transfused at study discharge: 0.82 ± 1.68 vs. 0.39 ± 1.50, adjusted difference 0.43 (−1.00; 0.15) for control vs STOP group, respectively, p = 0.02) (Table S4, Appendix p5).

Incidence of post-operative anaemia at the time of hospital discharge was similar in both groups at 90% and 98% respectively (Table 2) with higher Hb levels in the STOP group compared to control patients (11.1 ± 1.4 g/dL vs 10.3 ± 1.4 g/dL, adjusted difference: 0.80 g/dL, p < 0.01, Fig. 3, and Figure S3 Appendix p10). At this time, anaemia with iron deficiency was significantly lower in the STOP group (Table 2, Details on Iron Status in Table S5, Appendix p6). Incidence of anaemia within three months after hospital discharge was lower in the STOP group than in the control group: 30.4% vs 90.24% (OR 0.04 [95% CI: (0.01; 0.14)], p < 0.01) with higher Hb values (13.2 ± 1.14 g/dL *vs* 11.9 ± 1.1 g/dL
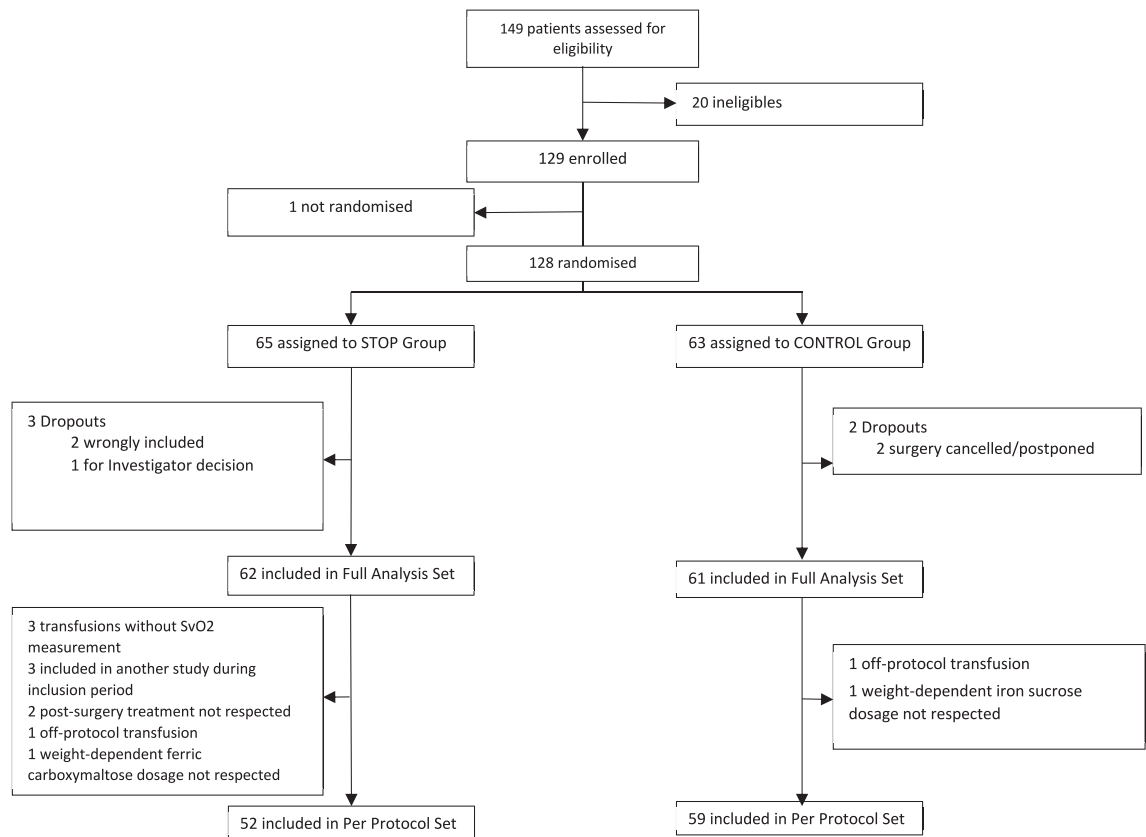
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Fig. 1: Flowchart.

respectively, adjusted difference: 1.23 g/dL, $p < 0.01$ (Table 2; Fig. 3).

There was no statistically significant difference between the two groups for any post-operative complications as well as ICU or hospital lengths of stay. One patient in the STOP group died two weeks after surgery from a refractory cardiac rhythm disorder (Table 3).

Total costs per patient related to anaemia treatment were higher in the STOP group than in the control group 367.8 ± 323.7€ vs 195.2 ± 346.6€ respectively ($p < 0.01$) (Table S6, Appendix p7).

Twelve AE, among them nine SAE occurred in the STOP group, and four AE, among them one SAE in the control group. None had been considered related to the study protocol by the independent trial safety committee.

Discussion

In this pilot study, we evaluated the efficacy of a bundle of care on transfusion and anaemia after cardiac surgery. The tested protocol included ultrashort pre-operative administration of FCM and EPO, individualised post-operative RBC transfusion guided by $ScvO_2$ and eventually post-operative FCM and EPO. Compared to the control group, the results showed a 50% reduction in post-operative RBC transfusion, an improved haemoglobin concentration at the time of hospital discharge and decreased anaemia incidence in the first 3 months after surgery from 90% to 30%.

Anaemia is a common deficiency seen in populations throughout the world that has raised concerns from the WHO which has issued several publications to create awareness on this "under-appreciated disease burden".[22] Detecting anaemia before surgery became a major issue in the concept of the PBM developed in the 2010s.[6,7,23] We have indeed observed a significant incidence of pre-operative anaemia (51%, 65/128), higher than previously reported.[1,2] The discrepancy between our results and anaemia incidence reported elsewhere (20–40%) may be explained by the TRUST score >3 as an inclusion criterion given anaemia is one of the data items taken into account in its calculation.

Treating pre-operative anaemia and optimising RBC mass may consist of iron supplementation, preferably intravenous, with or without iron deficiency, possibly associated with EPO.[6–8] This strategy has demonstrated good efficacy in reducing both transfusion and post-operative anaemia.[9,24] Even with a short lead time from screening to cardiac surgery, optimisation with

	Missing	Stop (n = 62)	Missing	Control (n = 61)	Difference [95% CI]
Age		70.5 (9.0)		69.7 (8.8)	0.8 (−2.4 to 4.0)
Sex					
Male		27 (44%)		27 (44%)	−0.7 (−18.3 to 16.8)
Female		35 (56%)		34 (56%)	0.7 (−16.8 to 18.3)
BMI (kg/m2)		25.6 (4.8)		25.1 (5.0)	0.5 (−1.2 to 2.3)
Pre-operative data					
Diabetes[a]	12	14 (28%)	9	11 (21%)	6.9 (−9.8 to 23.5)
Hypertension[a]	12	36 (72%)	9	37 (71%)	0.9 (−16.7 to 18.4)
Chronic obstructive pulmonary disease		15 (25%)		3 (5%)	20.1 (7.9 to 32.3)
Chronic kidney disease		11 (18%)		16 (26%)	−7.9 (−22.7 to 6.9)
Stroke		7 (11%)		6 (10%)	1.5 (−9.4 to 12.3)
Ischaemic heart disease		32 (52%)		24 (39%)	12.3 (−5.2 to 29.7)
Euroscore (%)		3.3 (2.6)		3.0 (±2.5)	0.4 (−0.6 to 1.3)
TRUST score		3.7 (0.8)		3.7 (0.7)	−0.03 (−0.3 to 0.2)
Plasma creatinine (umol/L)		95.4 (48.9)		99.7 (52.6)	−4.3 (−22.4 to 13.9)
Haemoglobin (g/dL)		13.0 (1.3)		12.7 (1.4)	0.3 (−0.1 to 0.8)
Surgery					
Coronary artery bypass		32 (52%)		30 (49%)	2.4 (−15.2 to 20.1)
Valvular surgery		36 (58%)		36 (59%)	−1.0 (−18.4 to 16.5)
Combined surgery		9 (15%)		9 (15%)	−0.2 (−12.7 to 12.3)
Redo surgery[a]	2	5 (8%)		2 (3%)	5.1 (−3.2 to 13.4)
Emergency surgery		3 (5%)		7 (11%)	−6.7 (−16.3 to 3.0)
Cardiopulmonary bypass time (min)		110.2 (43.8)		103.7 (42.1)	6.1 (−8.9 to 21.7)
Aortic clamp time (min)		84.9 (35.4)		78.8 (31.6)	6.1 (−5.9 to 18.0)
Any transfusion		17 (27%)		9 (15%)	12.7 (−1.6 to 26.9)
Red blood cells		15 (24%)		8 (13%)	11.1 (−2.5 to 24.7)
Fresh frozen plasma		10 (16%)		4 (7%)	9.6 (−1.5 to 20.6)
Platelets		1 (2%)		1 (2%)	−0.03 (−4.5 to 4.4)
Fibrinogen		3 (5%)		7 (11%)	−6.6 (−16.2 to 3.0)

Data are mean (SD) or n (%); BMI, Body Mass Index. [a]Data not available for all randomised patients. Only one significant difference: COPD was more frequent in the STOP group (p < 0.01).

Table 1: Patient characteristics (analysis set = FAS).

ultrashort treatment only few days before surgery has brought about fewer post-operative RBC transfusions with no side-effects.[11,12,25] In the present study, 25 patients in the STOP group (40.3%) could receive pre-operative FCM and EPO, suggesting that a good proportion of patients at risk of transfusion (TRUST score ≥3) may benefit from this strategy when delaying surgery is not possible to allow for a more complete anaemia treatment.[24]

Overall, the bundle of care in the STOP group succeeded in reducing RBC transfusion and optimising Hb concentration compared to controls. However, the relative impact of each component of the bundle of care is not equal. In the STOP group, transfusion was avoided due to $ScvO_2$ > 65% but only for one out of six post-operative anaemia events (16.7%). This proportion was lower than expected since previous studies reported more consistent RBC transfusion reduction (21–32%), but these trials used transfusion threshold higher than the present study (9 vs 8 g/dL).[15,16] The contribution of

transfusion adjustment with $ScvO_2$ on the benefits of post-operative transfusion therefore appears quite modest in this study. The transfusion exposure from ICU admission to hospital discharge was significantly decreased by 50% in the STOP group (from 31% to 14.5%), mainly because patients in this cohort had less severe anaemia than patients in the control group. Therefore, FCM and EPO administration seems to be the major contributor to the effectiveness of the bundle of care.

Pre-operative administration has already demonstrated a beneficial effect on post-operative transfusion in cardiac surgery.[11,12,25] The relative risk of being transfused when receiving pre-operative EPO, with or without iron supplementation was 0.55 [95% CI, 0.37–0.81] in a meta-analysis of nine studies in cardiac surgery with various therapeutic schemes (various EPO or iron supplementation doses, timing).[24] Even short-term pre-operative treatment has shown a significant impact on RBC transfusion with a RR varying from 0.44
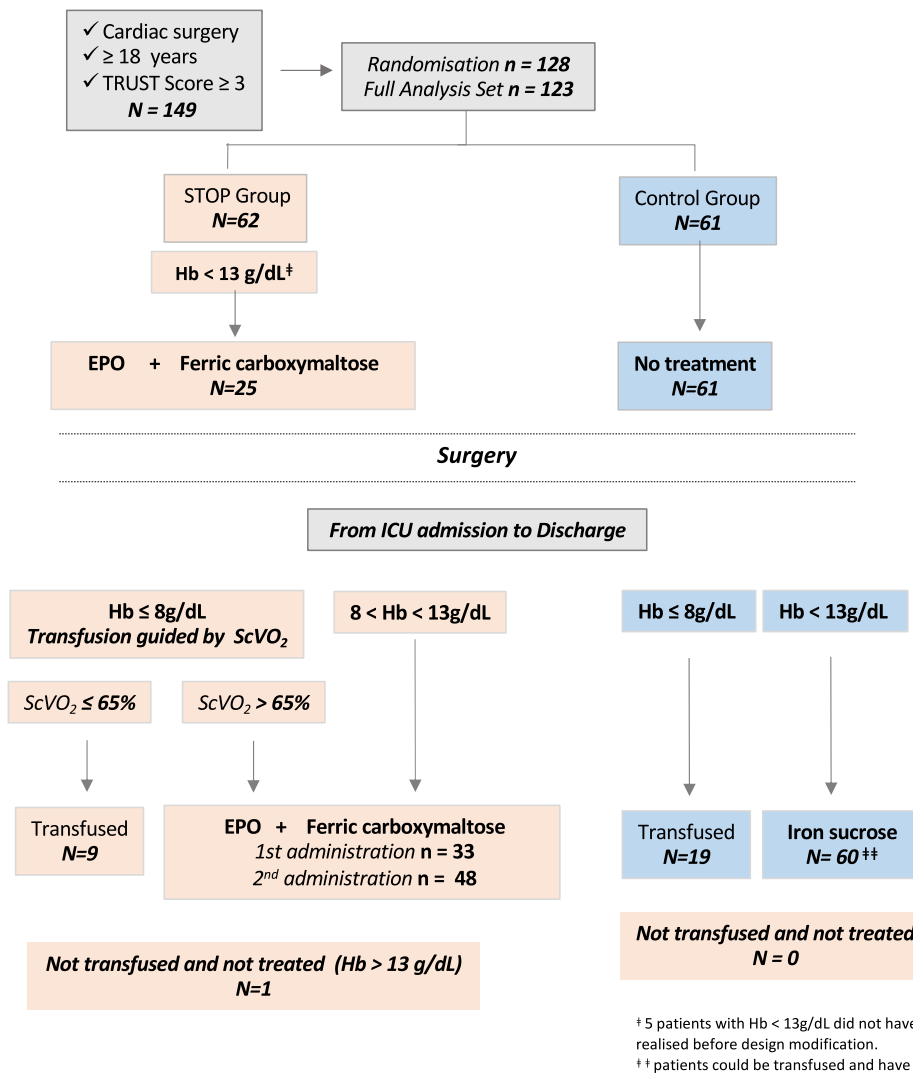
Fig. 2: Red blood cell transfusion and anaemia treatment distribution in control and STOP groups. Hb, Haemoblogin concentration; ICU, intensive Care Unit; EPO, erythropietin; ScVO₂, central venous oxygen saturation.

to 0.70, the best result being observed with the higher EPO dose.[11,12] Our results are close to the findings from the study by Luca Welter and co-workers[12] and even better when considering patients who did not undergo transfusion during surgery (RR 0.32 [95% CI 0.10–0.99]).

Post-operative EPO administration was also permitted in our study which differed from the study by Welter et al. In contrast to pre-operative administration, post-operative EPO administration has been barely evaluated and results from 2 previous RCT published in the early 2000s were not convincing.[26,27] There are several differences between the design of these two RCTs and ours including restrictive transfusion strategy, higher iron or EPO doses, timing of injections and patient selection with more exclusion criteria in

previous RCTs, which makes comparisons between studies challenging. Anyway, we cannot clearly estimate the impact of post-operative EPO alone on RBC transfusion from the results of our study. On the contrary, complementary FCM supplementation appeared more effective than iron sucrose in preventing iron deficiency at the time of hospital discharge (Table 2). Though the treatment induced a substantial iron load (up to 3N for plasma ferritin), it may have helped to lower iron deficiency and achieve a better Hb concentration a few months after surgery.

Besides RBC transfusion reduction, the effectiveness of the bundle of care was evaluated on Hb concentration. Restrictive Hb thresholds to decide RBC transfusion are strongly recommended by scientific societies.[6,7] However, if a restrictive transfusion strategy

	Stop (n = 62)	Control (n = 61)	Adjusted OR (95% CI)	p-value
Before surgery				
Anaemia	30 (48%)	35 (57%)	0.68 (0.33; 1.10)	0.30
Anaemia with iron deficiency[a]	19 (30.65%)	23 (38%)	0.70 (0.33; 1.51)	0.36
Anaemia without iron deficiency[a]	11 (18%)	11 (18%)	0.93 (0.36; 2.40)	0.89
Iron deficiency without anaemia[a]	12 (19%)	10 (17%)	1.25 (0.49; 23.23)	0.64
POD 1				
Anaemia	56 (90%)	60 (98%)	0.21 (0.04; 1.15)	0.07
Anaemia with iron deficiency	14 (23%)	8 (13%)	1.94 (0.75; 5.05)	0.17
Anaemia without iron deficiency	42 (68%)	52 (85%)	0.35 (0.14; 0.86)	0.02
Iron deficiency without anaemia	4 (6%)	0 (0%)	10.56 (0.73; 152.25)	0.08
Hospital discharge POD 28				
Anaemia	57 (92)	58 (97)	0.43 (0.10; 1.86)	0.26
Anaemia with iron deficiency[b]	10 (17.86)	40 (71.43)	0.08 (0.03; 0.20)	<0.01
Anaemia without iron deficiency[c]	41 (74.55)	14 (25.00)	9.06 (3.78; 21.70)	<0.01
Iron deficiency without anaemia[c]	2 (3.64)	1 (1.79)	1.66 (0.27; 10.17)	0.58
Within the first 3 months after hospital discharge				
Anaemia	14 (30%)	37 (90%)	0.04 (0.01; 0.14)	<0.01

Anaemia was initially defined as Hb concentration <13 g/dL. Iron deficiency (ID) was defined as ferritin concentration <100 μg/L or transferrin saturation coefficient <20%. Data are expressed as n (%). POD: Post-Operative Day. [a]Evaluated on 60 patients in the CONTROL group: ferritin concentration and transferrin saturation coefficient were not available for one patient in the CONTROL group to assess iron deficiency. [b]Evaluated on 56 patients in the STOP group and in 56 patients in the CONTROL group: 6 patients in the STOP group and 5 patients in the CONTROL group had anaemia at hospital discharge but ferritin concentration was not available to assess iron deficiency. [c]Evaluated on 55 patients in the STOP group and 56 patients in the CONTROL group: ferritin concentration was not available for 7 patients in the STOP group and 5 patients in the CONTROL group to assess iron deficiency.

Table 2: **Anaemia and iron status evolution (analysis set = FAS).**

helps to decrease transfusion rates, it elicits anaemia and may delay its correction which may be harmful specifically for older aged patients or severe cardiovascular disease.[14] Short-term pre-operative iron supplementation and EPO has shown, overall, a modest effect on post-operative Hb concentration in previous studies. However, these studies had limited Hb concentration monitoring up to the first post-operative week
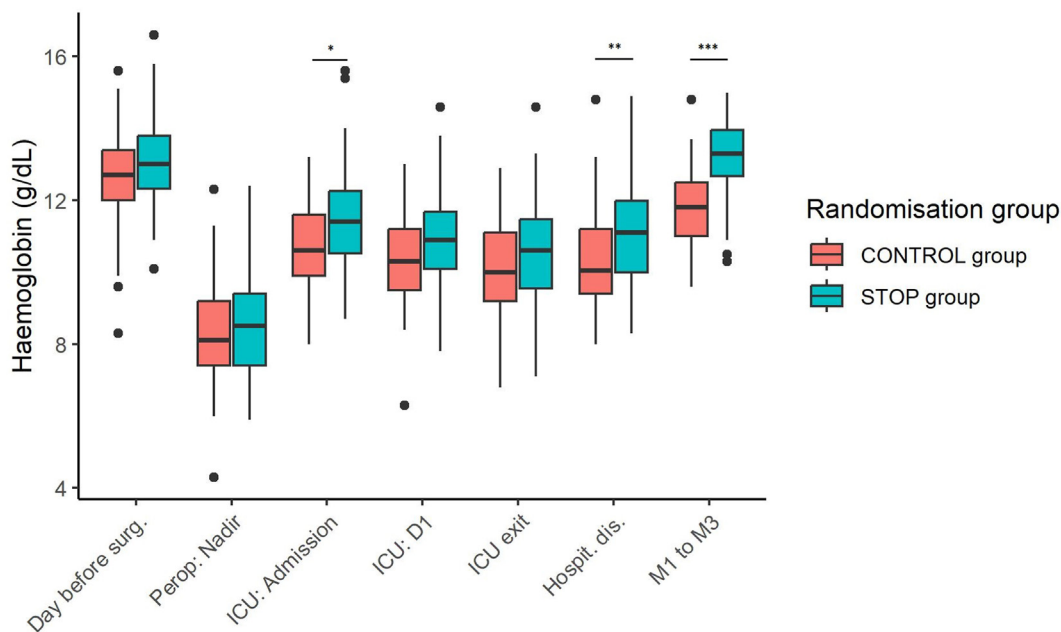

Fig. 3: Boxplots of haemoglobin content evolution (g/dL) in control and STOP groups. Haemoglobin content: on day before surgery, lowest peroperative concentration (nadir); postoperative concentration at ICU admission, at postoperative day 1 (ICU: D1), at ICU exit, at Hospital discharge (Hospit. Dis.). ICU, ntensive care unit. Data are expressed asmedian [Q3 + 1.5 IQR]. *p value < 0.05, **p value < 0.01, ***p value < 0.001.

	Stop group (n = 62)	Control group (n = 61)	p-value
ICU stay (days)			0.88
Mean (SD)	1.9 (2.5)	2.0 (±3.5)	
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	
Hospital stay (days)			0.91
Mean (SD)	11.5 (7.5)	10.98 (5.7)	
Median (IQR)	9.5 (7.0–13.0)	9.0 (7.0–14.0)	
Mortality rate at POD 28	1 (2%)	0 (0%)	1.00
Cardiac complications			
Exploration for bleeding	5 (8%)	4 (7%)	0.73
Atrial fibrillation	23 (38%)	15 (25%)	0.13
Conduction disorder	13 (21%)	11 (18%)	0.66
Low cardiac output syndrome	7 (11%)	11 (18%)	0.29
Acute kidney injury	2 (3%)	1 (2%)	0.59
Renal replacement therapy	1 (2%)	0 (0%)	0.38
Pulmonary infection	2 (3%)	2 (3%)	1.00
Sepsis	2 (3%)	3 (5%)	0.66
Thromboembolic events	4 (7%)	2 (3%)	0.42
Stroke	3 (5%)	0 (0%)	0.13
Pulmonary embolism[a]	1 (2%)	2 (3%)	0.58

POD: Post-Operative Day. [a]Evaluated on 61 patients in the STOP group and 60 patients in the CONTROL group. Analyses of post-operative complications were adjusted on BMI and sex (stratification factors).

Table 3: Secondary endpoints (from ICU admission to hospital discharge) (analysis set = FAS).

at most.[11,12,25] In our study, Hb concentration was significantly higher in the STOP group than in the control group at time of hospital discharge (meaning at median POD 9) and one to three months later. Consequently, post-operative anaemia (Hb < 13 g/dL) one to three months' post-hospital discharge affected 90.2% of patients in the control group but only 30.4% of patients in the STOP group. Expanding EPO and FCM treatment to the post-operative period may have contributed to this improvement.

The study population was too small to evaluate clinical outcomes but our observation did not show any differences between the two groups in terms of post-operative complications. Previous randomised studies on EPO and iron supplementation in cardiac surgery have revealed no safety concerns with this treatment.[11,12,28]

The transfusion costs were estimated by considering the quantity of RBC units, EPO and iron supplementation. In the STOP group, costs were mainly driven by FCM while RBC costs were reduced by half compared to the control group. Overall, the mean STOP strategy costs exceeded the standard one by €180.5 per patient (+92%). Since ferritin concentration was very high at the time of hospital discharge in the STOP group, the complementary FCM dose could have been reduced. Besides, indirect costs, such as those possibly related to long-term outcomes or quality of life, may have a budgetary impact on overall health expenditure.[29]

Our study has several limitations. It is a single centre exploratory study, with sample size too small to evaluate clinical outcomes such as mortality and postoperative

complications. The study was not blinded, and the SAP was approved at the end of the study, so that some bias cannot be fully excluded. We observed a trend for higher transfusion incidence during surgery in the STOP group patients compared to controls, even though transfusion management was guided by predefined rules and realized according to the decision made by the attending clinical team. However, in the sub-group analysis on patients who did not undergo transfusion during surgery, post-operative RBC transfusion incidence was significantly lower in the STOP group compared to controls. $ScvO_2$ was used as an adjustment variable to Hb concentration in the transfusion decision. However, $ScvO_2$ depends on several factors beyond Hb such as cardiac output, SaO_2 and VO_2. Moreover, circumstances such as sepsis or systemic inflammation where O_2 extraction is impaired may render $ScvO_2$ unreliable.

It is noteworthy that there were no missing data and very few protocol deviations, indeed the main result was corroborated by the sensitivity analysis on PP population, all of which enhances the strength of the study, beyond the randomisation process.

In conclusion, this pilot trial suggests that the studied bundle of care may notably reduce both RBC transfusion and post-operative anaemia in cardiac surgery. The findings should be interpreted with caution due to the unblinded and exploratory nature of the study, and need to be confirmed in a larger study, to also assess impact on clinical outcomes.

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