Patient blood management in elective bypass cardiac surgery: A 2-step single-centre interventional trial to analyse the impact of an educational programme and erythropoiesis stimulation on red blood cell transfusion

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ABSTRACT

Anaemia and iron deficiency are frequent in patients scheduled for cardiac surgery. Perioperative patient blood management (PBM) is widely recommended in current practice guidelines. The aim of this protocol is to analyse the effect of a global perioperative PBM programme on the red blood cell (RBC) transfusion ratio, morbidities and rehabilitation score in elective cardiac surgery.

This study is a prospective, single-centre trial with a 2-step protocol, A and B, as follows: A: non-drug intervention: the caregiver is given a blood management educational programme; B: drug intervention: systematic correction of perioperative iron, vitamin deficiencies, and anaemia. This study was designed to enrol 900 patients (500 in group A and 400 in group B) in a rolling period starting at anaesthesia consultation and ending 3 months after surgery. The primary objective was a 20% reduction in RBC transfusion after implementation of PBM programmes (protocol A + B) when compared to our previous transfusion ratio in the first half of 2018 (30.4% vs 38%). The secondary objectives were to evaluate the impact for each step of the study on the RBC transfusion rate, morbidity and the quality of postoperative rehabilitation.

The strength of this study is its evaluation of the effect of a global PBM programme on RBC transfusion in cardiac surgery through a 2-step protocol. We aim to assess for the first time the impact of non-drug and drug interventions on RBC transfusion, comorbidities and delayed rehabilitation parameters.

Trials registration: ClinicalTrials.gov, NCT04040023: registered 29 July 2019.

1. Introduction

The prevalence of anaemia in patients scheduled for elective cardiac surgery is approximately 25% [1]. Anaemia has been reported to be an independent risk factor for red blood cell (RBC) transfusion and adverse clinical outcomes, including infections, atrial fibrillation, respiratory complications, acute kidney injury and short-to-long-term mortality [2–6]. These adverse outcomes are directly proportional to the number

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of units of RBC transfused [3,4]. Furthermore, a previous study has shown that up to 37% of patients undergoing cardiac surgery had iron deficiency within two-thirds of them without anaemia and that they received more RBC transfusions perioperatively than patients without iron deficiency [7].

Therefore, numerous practice guidelines and consensus statements for perioperative patient blood management (PBM) have been proposed to reduce the risk of adverse outcomes associated with transfusions, bleeding, or anaemia [8–10]. The level of these recommendations is rather high despite a low level of publication on patient blood management in cardiac surgery. Research has revealed that adherence to these guidelines is poor, and as a result, a significant variability in patient transfusion practices among practitioners remains [9].

The aim of this study was to improve the relevance of RBC transfusion in cardiac surgery and to limit the morbidity and mortality induced by RBC transfusion. This study has a protocol of 2 successive steps (A and A + B). The first step (A) aims to analyse the impact of a caregiver blood management educational programme. The second step (A + B) analyses a drug programme based on a systematic assessment and treatment of anaemia and iron deficiency before and after elective cardiac surgery.

2. Materials and methods

2.1. Study design

Patient blood management in cardiac surgery is a single-centre, prospective superiority trial designed in two successive stages. The first programme (PBM initial, programme A) is a training programme for caregivers involved in cardiac surgery healthcare to implement new practice guidelines for perioperative blood management in cardiac surgery [8–10]. The second programme combines the training programme (programme A), whose information will be considered acquired, and a drug intervention programme (programme B) based on the systematic assessment and treatment of preoperative iron and vitamin deficiencies and anaemia.

Given the recruitment potential of our centre, we believe that each step of our study will take place in 6 months, taking into account potential exclusions and refusals of consent. The 2 steps will be separated by 2 months to ensure the smooth running of the 2nd programme (Fig. 1).

The Est III Ethical committee approved this protocol in July 2019 (No. 2019-A01522-55). The investigator presents information on the study in a letter that is given to the patient. To be enrolled, the patient must have expressed his oral consent to this study. This information is tracked in the medical computer charts. The trial protocol was registered online at ClinicalTrials.gov NCT04040023.

2.2. Inclusion and exclusion criteria

The inclusion criteria are all adult patients scheduled for elective cardiac surgery under cardiopulmonary bypass (CPB) who give oral consent to be enrolled in this trial.

The exclusion criteria are emergency cardiac surgery (<48 h) and contraindications or allergies to iron or erythropoietin treatment.

In practice, all patients seen in preoperative anaesthetic consultation for elective cardiac surgery under bypass will be invited to participate in this study. This consultation will occur approximately 3 weeks before surgery.

2.3. Study interventions

2.3.1. PBM initial programme (programme A)

The first programme is a caregiver educational programme. To this end, a training programme is delivered to medical and paramedical staff with 2-h courses every 2 months throughout the duration of the study. It is a non-drug intervention programme based on learning. This phase aims to sensitize health care staff to streamlining the transfusion by targeting the following points: limit perioperative and postoperative haemodilution; adapt the transfusion threshold (Hb < 8 g/dl) to the tolerance of the patient to anaemia in operative and postoperative periods; justify the use of RBC transfusion by setting up a questionnaire; and encourage the transfusion of RBC unit by unit. The aim of this first phase is to evaluate the impact of non-drug intervention on RBC transfusion and adverse clinical outcomes induced by this transfusion.

2.3.2. Drug intervention programme (programme B)

The second programme is based on a drug intervention programme to systematically assess and treat preoperative and postoperative iron, vitamin deficiencies and anaemia. Fig. 2 summarizes the preoperative drug intervention programme. Preoperative treatment is given on the day of anaesthetic evaluation (usually between 1 month and 1 week before the surgery). The treatment of preoperative iron deficiency consists of a slow (15 min) intravenous infusion of 20 mg/kg ferric carboxymaltose (maximum of 1000 mg, Ferinject®, Vifor France, Swiss) when ferritin <100 μg/l or ferritin <300 μg/l and transferrin saturation < 20%. Anaemia, defined by a haemoglobin <13 g/dl, is treated with 600 UI/kg subcutaneous erythropoietin α (Binocrit®, Sandoz, Autriche). In the case of vitamin B12 and oral folic acid deficiencies (i.e., <200 pg/mL for vitamin B12 and <5 ng/mL for oral folic acid), patients are
treated with 1 mg oral vitamin B12 per day for 15 days (CDM Lavoisier, France) and 5 mg oral folic acid (Speciafoldine®, Arrow, France) per day until the surgery. Additional explorations can be done at the discretion of the investigator.

In the postoperative setting, a systematic correction of iron deficiency induced by the surgery is used by ferric oxide–saccharose (Venofer®, ViforFrance, Swiss) with 300 mg at day 0 and 300 mg at day 2.

2.4. Data collection and follow-up

The patients’ baseline demographics and medical history will be collected. All patient data will be collected on a paper case report form (CRF) by the Data Manager. Data and original study forms will be entered and kept on file at the Clinique Pasteur. Participant files are stored in numerical order in a secure place. Participant files will be maintained in storage for a period of 15 years after completion of the study. The following data will be collected as scheduled (see Table 1): consent, medical history, complete biological assessments, quality of life, postoperative rehabilitation indicators, perioperative events and mortality. The quality of life and postoperative rehabilitation indicators will be quantified by the length of stay in intensive care, length of stay in hospital, need for rehospitalization, period recovery, EQ(5D) questionnaire [11], 6-min walk test [12] and NYHA class [13]. Patients will be followed up between the preoperative anaesthetic evaluation and 3 months after elective cardiac surgery, with three visits scheduled: at hospital discharge, at recovery discharge and at 3 months by a phone call.

Table 1
Standard protocol items.

| Inclusion | PreOP | Surgery | Discharge | Recovery | Phone call |
|-----------|-------|---------|-----------|----------|------------|
| HOSPITALIZATION | M-1 | D-1 | D0 | | 3 M |

Informed consent ✓
Verification of eligibility criteria ✓
Complete biological check-up ✓ ✓ ✓ ✓ ✓ ✓ ✓
(1)
Euroscore II ✓
NYHA ✓ ✓
6 min walk test ✓ ✓
EQ(5D) ✓ ✓
Collection of patient data ✓ ✓ ✓
Collection of treatments médicamenteux ✓ ✓ ✓ ✓ ✓ ✓
Collection of adverse events indésirables ✓ ✓ ✓ ✓ ✓ ✓ ✓

Complete biological check-up (1)
Ferritin, Transferrin saturation X
Holotranscobalamine X
Folic acid in erythrocyte X
Haemoglobin, plaquettes X X X X
Bleeding time, fibrinogen X X
Ionogram, Creatinine, eGFR, CRP, proteinemia X X X X
Irregular agglutinins X X
ß HCG (if necessary) X
Troponin X
NT-proBNP X

NYHA = New York Heart Association; EuroSCORE = European System for Cardiac Operative Risk Evaluation. eGFR = estimated glomerular filtration rate. CRP = C-reactive protein.
NT-proBNP = N-terminal pro-brain natriuretic peptide.
2.5. Outcomes

The primary endpoint is the transfusion rate, defined as the proportion of patients transfused by at least one RBC during the length of stay (starting at the day of surgery). The objective is to compare the RBC transfusion rate before and after the PBM complete programme (programme A + B).

Secondary endpoints are to evaluate the RBC transfusion rate for each step of the study (A and A + B). For each step, several outcomes will be evaluated: RBC transfusion during the stay (transfusion rate in our population); polytransfusion (defined as > 2 RBC transfusion/patient during the stay and/or transfusion of other blood products), post-operative bleeding (defined as the volume of bleeding obtained by drainage during the first 48 h postoperatively), morbidity and mortality at 3 months; the length of stay and need for rehospitalization; haemoglobin levels before, during and 3 months after hospitalization; peri-operative transfusion thresholds; quality of life and postoperative rehabilitation; and cost-benefit trade-off of the correction of iron deficiency when compared to RBC transfusion at the patient’s discharge from hospital.

Three-month morbidity and mortality will be measured using a “composite score” defined by the occurrence of one of the following adverse events within the first 3 postoperative months: infection (surgical site infection or bacteremia); thrombotic and ischaemic event (myocardial infarction, stroke, deep vein thrombosis/pulmonary embolism, mesenteric infarction); renal failure (increase of creatinine > 0.1 min−1 with a duration > 12 h; use of a positive inotropic drug such as dobutamine, epinephrine, milrinone or levosimendan) at any dose and for any duration; transfusional immunization (positive irregular agglutinins at 3 months); re-hospitalization for transfusion or for cardio-vascular events; and mortality.

2.6. Sample size estimation

**Group A Size:** As described above, 500 patients, corresponding to approximately 6 months of recruitment, will be enrolled in programme A. From this group of 500 patients, a subgroup (A5 group) will be secondarily defined as the programme A reference group, i.e., a group whose learning will be considered acquired (Table 2).

**Group B Size:** A sample of 320 patients is required to test the conformity of the transfusion rate of patients who received the PBM complete programme to the target value of 30.4% using a bilateral type I error of 5%.

The overall number of patients who have to be enrolled is therefore 900 patients.

2.7. Statistical methods

All statistical analyses will be thoroughly performed by independent statisticians who are not involved in patient treatment or outcome assessment. The statisticians will perform statistical analyses according to predetermined data handling and statistical methods, and there will be no arbitrary interference. All analyses will be performed on per-protocol (PP) and intention-to-treat (ITT) populations in accordance with the recommendations for superiority trials [14].

Baseline characteristics by group will be compared using descriptive analyses. All the statistical tests will be performed accounting for a bilateral type I error of 5%.

The primary endpoint analysis will be a conformity chi-square test for the reduction in RBC transfusion to less than 30.4%, which corresponds to a decrease of 20% or more in the actual transfusion rate (38% of RBC transfusion is the value observed at Clinic Pasteur in the first half of 2018).

A learning effect of programme A by the medical staff is expected in Table 2. In order to consider the group (Group A5) characterizing the first programme, it is important to check that this group is not biased by the learning effect. To do so, the group A5 is constructed sequentially from Group A: Group A patients will be subdivided into 100 size groups (Groups 1 to 5) chronologically by date of inclusion.

- Step 1. If the transfusion rate observed in group 1 is significantly different from the transfusion rate observed in groups 2–5, group 1 will be removed and we will proceed to step 2; otherwise, the A5 Group will consist of the consolidation of groups 1-2-3-4-5.
- Step 2. If the transfusion rate observed in group 2 is significantly different from the transfusion rate observed in groups 3 to 5, Group 2 will be removed and we will proceed to Step 3; otherwise, the A5 Group will be the 2 to 5 Group consolidation.
- Step 3. If the transfusion rate observed in group 3 is significantly different from the transfusion rate in groups 4 to 5, group 3 will be removed and we will proceed to Step 4; otherwise, the A5 Group will be the 3 to 5 Group consolidation.
- Step 4. If the transfusion rate observed in group 4 is significantly different from the transfusion rate observed in group 5, group 4 will be withdrawn, and group A5 will be made up of group 5; otherwise, group A5 will be consolidated into groups 4 and 5.

By removing chronologically groups for which learning is not proved, the procedure ensures the relevance of the group A5 as a group of patients characterizing programme A at the maximum of performances and thus a strong comparator group to Group B for assessing the performance of programme B. The comparison involved in the procedure is the chi-square test performed at a type I error of 5%.

The effect of the drug interventional programme (programme A + B) will be measured by comparing the values of the different endpoints involved in the protocol observed in Group B versus those observed in Group A5. These comparisons will be made by means of the chi-square homogeneity test or exact Fisher’s test for the qualitative variables and by means of the t-test or Mann-Whitney test for quantitative criteria.

### Table 2

**Flow chart of the different groups according to the intervention.** Example of two withdrawn groups corresponding to the learning curve of programme A. The A5 group corresponds to the acquired first programme.

| PBM initial (programme A) | PBM complete (Programme A + B) |
|---------------------------|---------------------------------|
| Group A                   | Group B                         |
| Group 1                   | Group 2                         |
| Current learning          | Current learning                |
| Group 3                   | Group 4                         |
| Current learning          | Acquired learning               |
| Group 5                   | Acquired learning               |

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The estimation of the different parameters listed in the “outcomes” section below from the data observed in Group B for the PBM complete programme and in Group A for programme A will be given punctually and by bilateral confidence intervals at the risk of 5%.

The impact of programme A on the parameters involved in the “outcomes” section will be analysed through the learning curves. The 5 samples (Groups 1 to 5) will be used to study the evolution in time of the parameters. The analysis will be conducted by the chi-square homogeneity test for qualitative criteria and one-way ANOVA for quantitative criteria. The effect of programme A will be assessed by means of a conformity chi-square test for the transition rate involving a target value of 38%.

Finally, concerning the cost-benefit objective, the values observed for the data of Group B for the PBM complete programme and A for programme A will be compared to the internal data of the clinic.

2.8. Ethical issues

The Est III Ethical committee approved this protocol in July 2019 (No. 2019-A01522-55). The investigator presents information on the study in a letter that is given to the patient. To be enrolled, the patient must have expressed his oral consent to this study. This information is tracked in the medical computer charts.

3. Discussion

The importance of blood conservation strategies in cardiac surgery is emphasized by the facts that anaemia is common in patients with cardiac disease and that cardiovascular surgical procedures have among the highest overall rate of RBC transfusion among all surgeries. For more than 20 years, the patient blood management (PBM) approach has been proposed and is now recommended to reduce alloimmune blood transfusion. Despite the publication of numerous guidelines and consensus statements on PBM in cardiac surgery [8-10,15,17], research has revealed that adherence to these guidelines is poor. Recent reports from the Society of Thoracic Surgeons [18,19] demonstrate a modest decline in blood product utilization in cardiac surgical procedures over the last decade, and alloimmune blood transfusions still occur in over 50% of high-risk cardiac surgery patients [20-22].

One of the complexities of cardiac surgery is that it comprises an interaction between the surgeon, the anaesthesiologist and the clinical perfusionist. The use of cardio-pulmonary bypass (CPB) distinguishes this discipline from other surgical specialties. The poor successful implementation of PBM in cardiac surgery may be due to the lack of standard management of CPB (priming solution, cardioplegia, point of care for coagulation monitoring, etc.) but also due to a lack of knowledge among physicians, lack of interdisciplinary commitment, and lack of human and initial financial resources.

The aim of this study is to evaluate the PBM programme in elective cardiac surgery by a two-stage protocol. The first programme is a training programme to sensitize health care staff to implement new practice guidelines for perioperative blood management in cardiac surgery [8-10]. The second programme combines the training programme considered acquired and a drug intervention programme based on the systematic assessment and treatment of preoperative and postoperative iron and vitaminic deficiencies and anaemia. As recommended by the new guidelines, this PBM programme is based on the optimization of the preoperative, intraoperative, and postoperative periods. This study is an interventional study in two successive stages to evaluate the impact of medical and paramedical learning in contrast to the drug substitution programme by haematopoietic stimulation. In fact, few studies have emphasized the potential effect of anaemia and iron deficiency treatment on reducing the red blood cell transfusion ratio and morbidity of patients undergoing elective cardiac surgery [23-26]. However, to our knowledge, no study has yet evaluated the importance of medical training focussed on perioperative optimization compared to the impact of haematopoietic stimulation before and after surgery.

In our protocol, perioperative optimization is based on the pre-, peri- and postoperative periods. The cornerstone of this optimization is also to emphasize the importance of teamwork between the surgeons, anaesthesiologists and clinical perfusionists to minimize bleeding and bleeding complications. In the first stage of our study, the preoperative evaluation included the identification of patients at high risk for postoperative bleeding and the management of patients on antithrombotic therapy. During cardiac surgery, intraoperative optimization is focussed on the limitation of haemodilution during CPB with the use of autologous priming, the routine use of cell salvage systems, heparin level over the conventionally used activated clotting time-guided heparin management (HMS plus, Medtronic system, France), the dose of protamine sulfate in a protamine-to-heparin dosing ratio driven by the HMS plus system, and the routine use of anti fibrinolytic therapy if there are no contraindications. Regarding fluid therapy, goal-directed haemodynamic evaluation therapy is used based on clinical and echocardiographic findings. Last but not least, a restrictive RBC transfusion is applied with a restrictive transfusion threshold (as strongly recommended) and with a restricted number of RBC transfusions (i.e., unit-by-unit with an interval revaluation except in case of haemorrhagic shock) [8,10,15,17,27].

In the second part of our protocol, a drug intervention programme based on the systematic assessment and treatment of iron, vitamin deficiencies and anaemia is applied. Iron deficiency is corrected with intravenous iron on the day of anaesthetic evaluation (usually 3 weeks before the surgery) and systematically after the surgery. In the preoperative period, the threshold to define iron deficiency is large (ferritin <100 μg/l or ferritin <300 μg/l and transferrin saturation <20%), as used in the FAIR and CONFIRM HF studies [28,29], and the correction is effective with or without anaemia. In cases of anaemia with or without iron deficiency, erythropoiesis-stimulating agent is injected per week until the surgery. Last, vitamin B12 and oral folic acid are also corrected if appropriate.

Our study was designed to evaluate the impact of PBM during the hospital stay but also at discharge for cardiac rehabilitation and at 3 months. To the best of our knowledge, this is the first study to involve cardiac rehabilitation centres in the PBM programme. Only one study was interested in identifying the iron deficiency patterns at admission to a cardiac rehabilitation programme [30]. They have shown that absolute iron deficiency following cardiac surgery is more frequent in heart valve surgery and is associated with a prolonged hospital stay. Except for this trial, no studies in cardiac surgery have evaluated the impact of those treatments in the long term.

4. Conclusions

We are currently enrolling patients in a large prospective single centre interventional 2-step study to analyse the effect of a caregiver blood management educational programme with and without a haematopoietic stimulation (including EPO in anaemic patients) and the effect on blood transfusion, morbi-mortality and rehabilitation in elective cardiac surgery.

As of February 28 2020, 380 patients were enrolled, and recruitment is ongoing. A total of 900 patients will be recruited for the trial within 22 months. The recruitment of patients started in September 2019 and will finish in July 2021.

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