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**ORIGINAL ARTICLE**

# Pre-Operative Intravenous Iron Therapy in Patients Undergoing Coronary Artery Bypass Surgery on Cardiopulmonary Bypass: A Non-Randomized Study

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## Abstract

**Objective:** To study if preoperative iron and vitamin $B_{12}$ supplementation in anaemic patients undergoing coronary artery bypass graft (CABG) surgery would reduce transfusion requirements perioperatively. **Materials and methods:** In this prospective non-randomised study, consenting patients received 20 mg/kg of ferric carboxymaltose intravenously and 1-mg of vitamin $B_{12}$ subcutaneously (treatment arm). The control arm did not receive supplements. The primary outcome was perioperative transfusion requirement. Secondary outcomes included duration of ventilation and intensive care stay. The difference in transfusion requirements, haemoglobin and length of stay were assessed using Chi-square and Fisher's exact test as appropriate. Factors associated with ≥2 red cell (RBC) transfusions were explored using bivariate and multivariate logistic regression analysis and expressed as odds ratio (OR) with 95% confidence intervals (CI). **Results**: The mean (SD) age of the cohort was 61 (8) years; 79% were males. Baseline heart rate, body mass index, blood pressure, co-morbidities and creatinine were similar in the treatment (n=45) and control (n=159) arms. The median (IQR) EuroSCORE-II was 0.94 (0.7-1.2) in cases and 0.93 (0.7-1.3) in controls. The median preoperative hemoglobin was 11.6 (11.1-12.5) g/dl and not different (p=0.63) in cases and controls. RBC transfusion requirement was similar (p=0.69) perioperatively in cases (1.38 (1.11) units) and controls (1.46 (1.17)). Fresh frozen plasma (p=0.98) and platelet (p=0.13) transfusions were similar in both groups; 4 patients needed cryoprecipitate. On multivariable logistic regression analysis, female gender (OR 2.76, 95%CI 2.16-14.7), higher EuroSCORE-II (3.77, 1.53-9.31) and longer cross-clamp time (1.04, 1.01-1.06) were independently associated with the need for ≥2 RBC transfusions perioperatively. **Conclusions**: The acute preoperative administration of ultra-short acting iron and vitamin $B_{12}$ in patients undergoing CABG surgery did not reduce perioperative transfusion requirements. Several factors were associated with the need for ≥2 RBC transfusions.

**Keywords:** Anaemia, transfusion, iron; vitamin $B_{12}$, outcome, cardio-pulmonary bypass surgery

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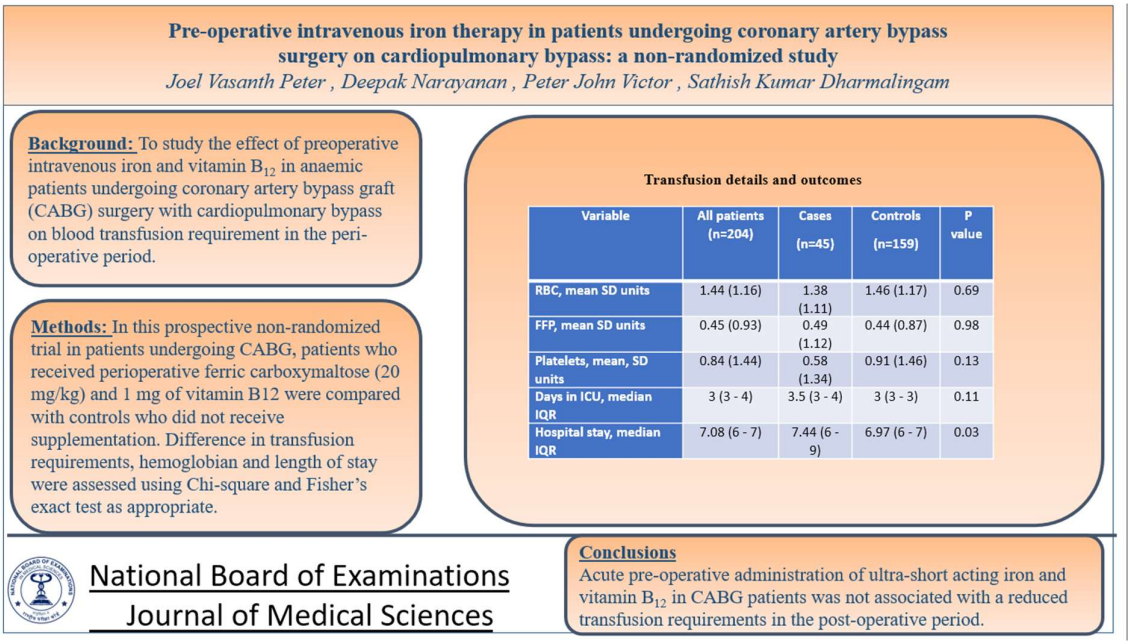
## Graphical Abstract




## Introduction

Anaemia contributes to perioperative morbidity and mortality in patients undergoing coronary artery bypass graft (CABG) surgery. In a large study from Italy of 4594 patients who underwent CABG, a linear relationship between the severity of anaemia and mortality was demonstrated, with mortality of 3.4% in patients without anaemia and 7.7% and 15.7% in mild and moderate to severe anaemia respectively [1]. In another cohort involving 3500 patients in Canada [2], the prevalence of anaemia, defined as haemoglobin <12.5 g/dl, was 26%. The composite outcome of in-hospital death, stroke, or acute kidney injury (AKI) was significantly higher in patients with anaemia and was independently associated with worse outcomes [2].

Given the association between anaemia and perioperative outcomes in patients undergoing CABG, it appears intuitive to correct anaemia prior to subjecting the patient to surgery. Correction of anaemia would involve assessing the cause and initiating appropriate treatment. Although anaemia due to deficiency (e.g., iron, vitamin $B_{12}$, folic acid) could be effectively treated with nutritional supplementation, anaemia due to other causes (e.g., chronic kidney disease (CKD), anaemia of chronic disease) may be difficult to correct. Delaying surgery while waiting for the haemoglobin to improve in nutritional deficiencies may pose risk to patients with significant coronary artery disease (CAD).

The gold standard for the treatment of anaemia in the perioperative period is blood transfusions. However, blood transfusions can be associated with early complications such as haemolytic reactions, non-haemolytic febrile reactions, allergies and anaphylaxis, acute lung injury, fluid overload and hyperkalaemia as well as delayed complications such as infections, iron overload and immune sensitisation [3,4]. There is also evidence that the greater

the number of blood transfusions, the higher the mortality and morbidity [3,4].

In this context, there has been interest in the ultra-short-term use of a combination of iron, vitamin $B_{12}$ and erythropoietin prior to surgery. In a single study of 1006 patients with preoperative anaemia or isolated iron deficiency anaemia who were scheduled to undergo cardiac surgery [5], ultra-short-term combination treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin $B_{12}$ and oral folic acid reduced red blood cell [5] and total allogeneic blood product requirements in the post-operative period, with the effect lasting for 90 days [5].

This non-randomized prospective study was undertaken to evaluate if preoperative administration of intravenous iron carboxymaltose and vitamin $B_{12}$ would reduce perioperative transfusion requirements in patients with anaemia who are undergoing CABG surgery on cardiopulmonary bypass pump when compared with patients who were not treated with supplements.

## Patients and Methods

### *Setting and study design*

This prospective non-randomized study was undertaken in a tertiary care teaching hospital in India between September 2021 and November 2022 on patients who were posted for CABG and were found to be anaemic. Anaemia was defined as haemoglobin <12 g/dl in women and <13 g/dl in men. The treatment arm comprised of patients undergoing CABG who consented to participate. They received ferric carboxymaltose intravenously and vitamin $B_{12}$ subcutaneously preoperatively. The control arm did not receive supplements. Although this study was planned as a randomized controlled clinical trial, due to logistic issues, this study was undertaken as a cohort study with two arms.

### *Inclusion and exclusion criteria*

Patients undergoing CABG without any valve replacement with the following characteristics, age 18 – 90 years, ASA 2, 3 and 4 and ejection fraction of >40% were considered for inclusion. Exclusion criteria were those with a known bleeding disorder, revision surgery, ASA 5 and above, age <18 years and >90 years, allergy to intervention drugs, emergency CABG surgery, patients undergoing off-pump CABG, patients with severe anaemia (<8 g/dL), and postoperative revision surgery due to hemopericardium or sternal wound infection.

### *Patient recruitment*

Patient were recruited after they were posted in the elective cardiothoracic surgery list. Patients were approached by the principal investigator (PI) prior to surgery and the study was explained in detail. An information sheet was also provided in the language that they understood. If the patient agreed to participate in the study, signed consent was obtained. Other patients with anaemia, who underwent CABG and who were either unwilling to receive the study drugs or were not recruited due to logistic issues were enrolled to the control arm. The treatment protocol was similar for all patients.

### *Data collection*

Data collected included demographics, treatment details and outcomes. Demographic data included age, gender, height, weight, body mass index (BMI), co-morbidities and habits (smoking, alcohol). Baseline heart rate (HR) and

blood pressure (BP) were recorded. Complete blood examination, renal and liver function tests and coagulation parameters were done preoperatively. EuroSCORE II was calculated for all patients [1].

Intraoperative and postoperative data on the use of inotropes, time of extubation, and length of stay (LOS) in ICU and hospital were recorded. The vasoactive-inotropic score (VIS), a composite index of quantum of vasoactive agents used [6], was calculated for all patients.

The number of units of red blood cells (RBC), platelets, FFP, and cryoprecipitate that were transfused during surgery and postoperative period were recorded. Data sheets were kept in the patient's hospital folder, so that intraoperative details could be filled by the attending anaesthesiologist. It was collected after the patient reached the intensive care unit (ICU) and was followed up by the PI till discharge.

***Outcome parameters***

The primary outcome was the need for RBC transfusions in the perioperative period. Secondary outcomes included postoperative haemoglobin, duration of mechanical ventilation and ICU and hospital LOS. The need for other blood products (platelets, fresh frozen plasma, cryoprecipitate) was recorded.

***Administration of study drugs***

The study drugs were administered at least 48-h prior to the surgery. The intravenous iron was given at 20 mg/kg (up to a maximum of 1 g) in 100 ml of normal saline over 2-h under monitoring. Patients also received 1-mg of subcutaneous vitamin $B_{12}$ prior to the iron.

***Anaesthesia and surgery protocols***

During surgery, intravenous access was established and standard monitoring devices (electrocardiography, pulse oximetry, end-tidal $CO_2$ monitoring, invasive arterial BP monitor) were placed prior to induction of anaesthesia. The standard protocol involved the intravenous administration of injection fentanyl 2-3 mcg/kg and propofol 1-2 mg/kg, and, vecuronium 0.1 mg/kg or rocuronium 1.5 mg/kg for induction. After intubation, central venous access was obtained through the internal jugular vein using an 8.5 Fr quad lumen. Anaesthesia was maintained with balanced air, oxygen, and isoflurane (0.8 to 1 MAC). Intra-operatively, boluses of fentanyl or morphine were given to decrease the pain response. Paracetamol was also administered intra-operatively.

The BP was titrated intraoperatively with noradrenaline, adrenaline, and glyceryl trinitrate. Hypotension was treated with phenylephrine or ephedrine boluses. The cross-clamp time and the cardio-pulmonary bypass (CPB) time was noted by the perfusionists who were managing the patient during the CPB period intraoperatively. Heparin was given prior to going on CPB based on the body weight and titrated to >3 times the baseline or at least 450 sec.

Blood was transfused based on the haemoglobin on the arterial blood gas (ABG) that was taken at while on bypass and after coming off bypass. The cut-off for transfusion was <7.0 g/dL during CPB and <8g/dL after CPB. After coming off bypass, protamine was administered in the ratio of 1:1.2 to 1:1.4 to bring ACT to baseline. FFP and platelet transfusions intraoperatively were based on clinical parameters such as a wet field with no active bleeder, adhesion of mediastinal structures, preoperative low

platelets, and recent intake of clopidogrel or preoperative liver derangements (rare) and laboratory coagulation parameters done intraoperatively. Once haemostasis was achieved, the patient was transferred to the ICU with the endotracheal tube in situ.

Once extubation criteria were fulfilled, the patient was extubated. The supports were gradually weaned off and, if necessary, blood and blood products were administered according to the laboratory and clinical parameters. Once the patient was stable, he/she was discharged to the ward. When fit for discharge, the patient was asked to review after 3-4 weeks with a repeat haemoglobin.

***Statistical methods***

Sample size calculations were done as for a randomised trial assuming that 70-80% of anaemic patients would require perioperative RBC transfusion. To detect a 15% difference in the transfusion requirement with supplements, 100 patients needed to be recruited in each arm, assuming 80% power. Summary data was presented as mean (standard deviation, SD) for continuous variables with normal distribution and as median with interquartile range (IQR) if data was skewed. Categorical variables were presented as numbers and percentages The difference in transfusion requirements, haemoglobin and length of stay were assessed using Chi-square and Fisher's exact test as appropriate. Factors associated with need for ≥2 RBC transfusions were explored using bivariate logistic regression analysis and reported as unadjusted analysis. Clinically and statistically significant factors were incorporated in a multivariable logistic regression analysis. Statistical significance was defined as $p<0.05$. All analyses were performed using Statistical Package for Social Sciences for Windows (SPSS) v25 and STATA™ v16.

***IRB and ethics committee approval details***

The study was approved by the Institutional Review Board (IRB No. 13821, 24.02.2021). The interventional medications were provided from the approved funds.

**Results**

***Baseline characteristics***

During the study period, 723 patients were screened. Of these, 519 patients were excluded (Figure 1). Of the 204 patients who were considered suitable for inclusion, 159 did not receive the intervention and were taken as controls (control arm). Of the 65 patients who consented to participate in the trial, 45 received the intervention (treatment arm); 18 patients were excluded due to cancellation of surgery, re-exploration and surgeon unwilling for patient to receive the intervention. Another 2 patients were lost to follow up.

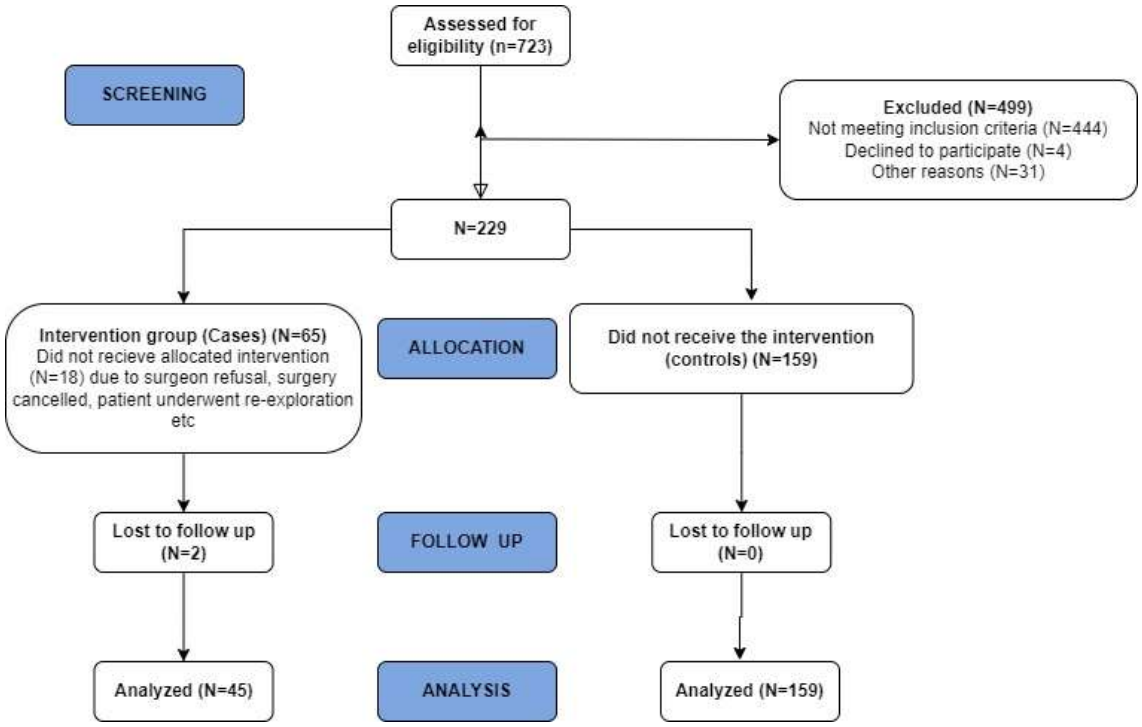


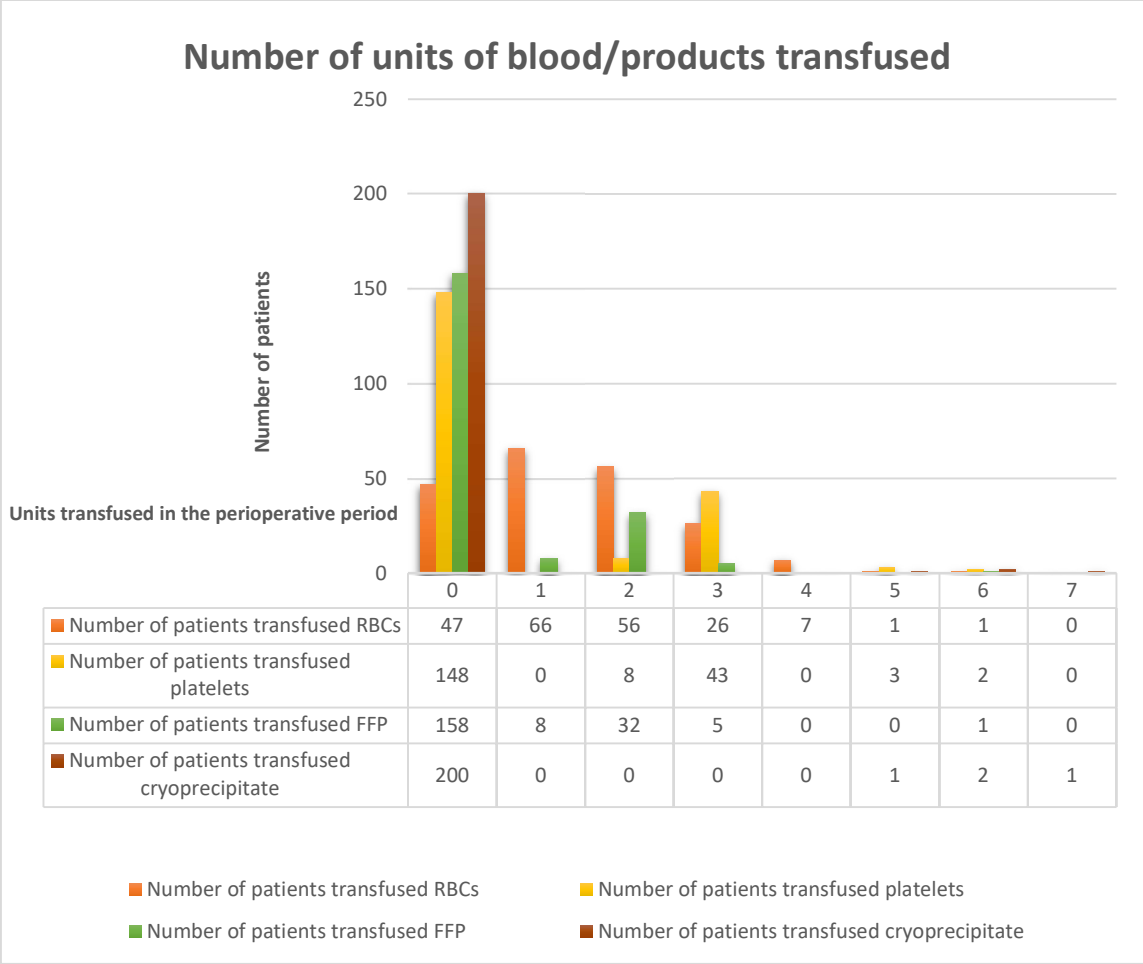

Figure 1. Strobe diagram of patients screened and included.
Strobe diagram shows the number of patients who were screened and the number who were finally analysed. Of the 723 patients who were assessed for eligibility, 499 patients were excluded for not meeting inclusion criteria (n=444), declining to participate (n=4) and other reasons (n=31). Of the remaining 224 patients, 65 were included in the treatment group. Of these, 18 did not receive the treatment and 2 patients were lost to follow-up. The treatment arm hence had 45 patients. The remaining 159 patients were controls

(SD) serum creatinine was 1.1 mg/dL (0.86). When patients were categorized according to the ASA grade, a majority (81.4%) were Grade 3. A majority (73%) had normal left ventricular ejection fraction (EF) and 27% had mild left ventricular systolic dysfunction (EF 40-49%).

***Treatment details***

All patients had significant obstruction of the left anterior descending artery that required grafting. The other vessels that were grafted were obtuse marginal artery (n=167), posterior descending artery (n=87), right coronary artery (n=33), diagonal branches (n=29), ramus intermedius (n=27) and the postero-lateral artery (n=9).

Transfusion details are summarized in Figure 2. Overall, 47 patients did not require RBC transfusion; the rest required between one and six units of transfusion, with a majority (n=66) requiring one unit during surgery (Figure 2). Platelet transfusion was required in 56 patients (2 units 8 patients, 3 units 43 patients). FFP was transfused in 46 patients; a majority required two units of FFP while 13 patients required either 1 or 3 units. Cryoprecipitate was required in 4 patients (2 %).




| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| Number of patients transfused RBCs | 47 | 66 | 56 | 26 | 7 | 1 | 1 | 0 |
| Number of patients transfused platelets | 148 | 0 | 8 | 43 | 0 | 3 | 2 | 0 |
| Number of patients transfused FFP | 158 | 8 | 32 | 5 | 0 | 0 | 1 | 0 |
| Number of patients transfused cryoprecipitate | 200 | 0 | 0 | 0 | 0 | 1 | 2 | 1 |

Figure 2. Blood product transfusions

Figure shows the number of patients who received the specific units of transfusion in the y axis. The x axis denotes the number of units transfused (ranging from 0 to 7) of a product (red blood cell (RBC), fresh frozen plasma (FFP), platelets and cryoprecipitate), each of which is colour coded. Of the 204 patients in the study, no RBC transfusion was required in 47 patients, while no platelets, FFP and cryoprecipitate transfusions were required in 148, 158 and 200 patients respectively. One unit of RBC transfusion was required in 66 patients while 56 patients required 2 units; 35 patients needed 3 or more RBC transfusions.

**Comparison of cases and controls**

Exploratory analysis was undertaken to compare several variables between cases and controls. Baseline characteristics and comorbidities were similar in the treatment and control arms (Table 1). Clinical variables, baseline investigations and EUROSCORE-II were also not different between cases and controls (Table 2). The low EUROSCORE-II suggests that patients were low risk for surgery.

The mean (SD) number of RBCs that was transfused was 1.4 (1.16) units (Table 3). There was no significant difference in the number transfused between cases and controls (p=0.69). Since the primary outcome was not different between cases and controls, no further exploratory analysis was performed. The

requirement of FFP was only 0.45 (0.93) units and similar between the two groups (p=0.98). Similarly, the requirement of platelets was 0.84 units (1.44) and not different between cases and controls (p=0.13).

Table 1. Summary of baseline characteristics between cases and controls

| Variable | All patients (n=204) | Cases (n=45) | Controls (n=159) | P value |
|---|---|---|---|---|
| Age, mean (SD) years | 61.0 (8) | 60.5 (8.4) | 61.0 (7.9) | 0.67 |
| Gender, M: F (% M) | 162:44 (79.0) | 33:12 (73.3) | 129:31(80.6) | 0.29 |
| Height, mean (SD) cm | 161.6 (8.7) | 161.2 (8.7) | 161.7 (8.8) | 0.73 |
| Weight, mean (SD) kg | 63.3 (10.6) | 63.2 (10.6) | 63.3 (10.6) | 0.95 |
| BMI, mean (SD) kg/m2 | 24.3 (3.29) | 24.5 (3.35) | 24.2 (3.28) | 0.67 |
| Diabetes mellitus | 144 (70.6) | 33 (73.3) | 111 (69.8) | 0.71 |
| Hypertension | 143 (70.1) | 27 (60.0) | 116 (74.9) | 0.10 |
| Bronchial asthma | 5 (2.5) | 1 (2.2) | 4 (2.5) | 1.0 |
| Chronic kidney disease | 8 (3.9) | 3 (6.7) | 5 (3.9) | 0.38 |
| Dyslipidaemia | 26 (12.8) | 7 (15.6) | 19 (12.0) | 0.61 |

SD – Standard deviation

Table 2. Clinical and laboratory variables at recruitment

| Clinical variables | All patients (n=204) | Cases (n=45) | Controls (n=159) | P value |
|---|---|---|---|---|
| Heart rate, beats/min | 74.6 (65 - 85) | 75.3 (65 - 85) | 74.4 (65 - 85) | 0.71 |
| Systolic BP (mm Hg) | 135 (120 - 150) | 134 (120 - 140) | 135 (120 - 150) | 0.61 |
| Diastolic BP (mm Hg) | 80.0 (70 - 85) | 79.4 (70 - 85) | 80.1 (70 - 85) | 0.67 |
| MAP, mean, SD | 98.3 (9.5) | 97.7 (8.5) | 98.5 (9.8) | 0.63 |
| EUROSCORE-II | 0.93 (0.7 - 1.3) | 0.94 (0.7 - 1.2) | 0.93 (0.7 - 1.3) | 0.40 |
| Haemoglobin, g/dl | 11.6 (11.1 - 12.5) | 11.5 (11.1 - 12.3) | 11.7 (11.2 - 12.6) | 0.63 |
| MCV, mean, SD | 86.0 (81.6 – 91.0) | 85.6 (81.1 - 90.5) | 86.1 (82.7 - 91.4) | 0.70 |
| Platelets (x $10^5$) | 2.21 (1.54 – 2.67) | 2.32 (1.81 – 2.73) | 2.81 (1.51- 2.66) | 0.23 |
| PT | 14.4 (13.5 - 15.2) | 14.6 (13.4 - 15.4) | 14.4 (13.6 - 15.1) | 0.51 |
| PT (INR) | 1.07 (0.99 - 1.12) | 1.07 (0.97 - 1.15) | 1.06 (0.99 - 1.11) | 0.55 |
| APTT | 34.1 (30.9 - 36.1) | 33.2 (30 - 36.1) | 34.4 (31.1 - 36.1) | 0.19 |
| Creatinine | 1.11 (0.82 - 1.16) | 1.04 (0.78 - 1.09) | 1.13 (0.83 - 1.17) | 0.53 |
| Creat. clearance | 71.7 (54.1 - 86.9) | 72.7 (53.8 - 91.8) | 71.5 (54.1 - 86.1) | 0.78 |

All values are median interquartile range unless specified, MAP mean arterial pressure, MCV mean corpuscular volume, PT prothrombin time, INR international normalized value, APTT activated partial thromboplastin time, SD standard deviation.

Table 3. Transfusion details and outcomes

| Variable | All patients (n=204) | Cases (n=45) | Controls (n=159) | P value |
|---|---|---|---|---|
| RBC, mean SD units | 1.44 (1.16) | 1.38 (1.11) | 1.46 (1.17) | 0.69 |
| FFP, mean SD units | 0.45 (0.93) | 0.49 (1.12) | 0.44 (0.87) | 0.98 |
| Platelets, mean, SD units | 0.84 (1.44) | 0.58 (1.34) | 0.91 (1.46) | 0.13 |
| Days in ICU, median IQR | 3 (3 - 4) | 3.5 (3 - 4) | 3 (3 - 3) | 0.11 |
| Hospital stay, median IQR | 7.08 (6 - 7) | 7.44 (6 - 9) | 6.97 (6 - 7) | 0.03 |

SD standard deviation; IQR interquartile range, RBC red blood cell transfusion, FFP fresh frozen plasma, ICU intensive care unit.

The duration of ICU stay was similar between cases and controls (p=0.11). However, the duration of hospital stay post-surgery was marginally but significantly higher in controls (P=0.03) when compared with cases.

***Factors associated with more than one unit of RBC transfusion***

Exploratory analysis was undertaken to evaluate for factors associated with the need for >2 units of RBC transfusion. On bivariate logistic regression analysis (Table 4a), factors associated were increasing age (OR 1.05, 95%CI 1.02 to 1.10), female gender (OR 3.95, 95%CI 1.92 to 8.12), higher EuroSCORE-II (OR 3.50, 95%CI 1.84 to 6.67), pre-operative haemoglobin (OR 5.64, 95%CI 2.72 to 11.72), cross-clamp time (OR 1.02, 95%CI 1.0 to 1.04), number of platelets transfused (OR 1.35, 95%CI 1.11 to 1.65) and number of FFP transfused (OR 1.73, 95%CI 1.23 to 2.43). The need for ≥2 RBC transfusion was associated with longer duration of hospital stay following surgery (OR 1.19, 95%CI 1.04 to 1.36) but not with increased ICU LOS (OR 1.14, 95%CI 0.69 to 1.91).

On multivariable logistic regression analysis (Table 4b), female gender (OR 2.76, 95%CI 2.16 to 14.7), higher EuroSCORE II (OR 3.77, 95%CI 1.53 to 9.31) and longer cross-clamp time (OR 1.04, 95%CI 1.01 to 1.06) were independently associated with need for 2 or more units of RBC transfusion during the perioperative period. Platelet and FFP transfusions were not incorporated in the model due to co-linearity in the relationship between the need for red cells and platelet and FFP transfusions.

Table 4 a. Bivariate analysis of factors associated with ≥2 RBC transfusion.

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| Age | 1.05 | 1.02 to 1.10 | 0.006 |
| Female gender | 3.95 | 1.92 to 8.12 | <0.001 |
| EuroSCORE II | 3.50 | 1.84 to 6.67 | <0.001 |
| NYHA class of symptoms | 1.28 | 0.52 to 3.14 | 0.59 |
| Number of vessels diseased | 1.61 | 0.83 to 3.15 | 0.16 |
| Ejection fraction on ECHO | 1.00 | 0.96 to 1.04 | 0.97 |
| Pre-operative haemoglobin~ | 5.64 | 2.72 to 11.72 | <0.001 |

| | | | |
|---|---|---|---|
| Pre-operative iron/vitamin B12^ | 1.00 | 0.52 to 1.95 | 0.99 |
| Baseline MAP | 0.97 | 0.95 to 1.00 | 0.09 |
| Baseline heart rate | 1.02 | 1.00 to 1.05 | 0.11 |
| Time on CPB | 1.01 | 1.00 to 1.02 | 0.11 |
| Cross clamp time | 1.02 | 1.00 to 1.04 | 0.054 |
| Vasoactive inotrope score | 1.04 | 0.93 to 1.16 | 0.51 |
| Number of platelets transfused | 1.35 | 1.11 to 1.65 | 0.003 |
| Number of FFP transfused | 1.73 | 1.23 to 2.43 | 0.002 |
| Duration of ICU stay | 1.14 | 0.69 to 1.91 | 0.59 |
| Duration of hospital stay* | 1.19 | 1.04 to 1.36 | 0.012 |

Table 4b. Multivariate analysis of factors associated with ≥2 RBC transfusion.

| Variable | Odds ratio | 95% confidence interval | P value |
|---|---|---|---|
| Age | 1.03 | 0.98 to 1.08 | 0.31 |
| Female gender | 2.76 | 2.16 to 14.7 | <0.001 |
| EuroSCORE II | 3.77 | 1.53 to 9.31 | 0.004 |
| Cross clamp time | 1.04 | 1.01 to 1.06 | 0.006 |
| Duration of hospital stay | 1.02 | 0.87 to 1.23 | 0.71 |

*Hospital stay is post-surgery; MAP mean arterial pressure, CPB cardiopulmonary bypass; ICU intensive care unit; FFP fresh frozen plasma; NYHA New York Heart Association; ^peri-operative administration of iron/vitamin $B_{12}$

**Discussion**

In this non-randomized study of patients with anaemia and undergoing CABG using CPB, acute preoperative administration of iron and vitamin $B_{12}$ did not reduce transfusion requirements in the perioperative period. The mean number of RBC transfusion was similar in the treatment (1.38, SD 1.11) and control (1.46, 1.17) arms as was the requirement for FFP (p=0.98) and platelets (p=0.13). On multivariable logistic regression analysis, female gender (OR 2.76, 95%CI 2.16 to 14.7), higher EuroSCORE-II (OR 3.77, 95%; CI 1.53 to 9.31) and longer cross-clamp time (OR 1.04, 95%CI 1.01 to 1.06) were independently associated with the need for ≥2 RBC transfusions perioperatively.

It is recognized that anaemia is not infrequent in patients with CAD and that it can contribute to perioperative morbidity and mortality in those undergoing CABG surgery. In the cohort study from Canada enrolling 3500 patients undergoing CABG, the prevalence of preoperative anaemia was 26% [2]. Anaemia was significantly associated with in-hospital death, stroke, and AKI [2]. In the study from Italy that included 4594 patients, the mortality was 3.4% in patients without anaemia while it ranged from 7.7 to 15.7% in those with mild and moderate to severe anaemia [1]. Thus, there appears to be merit in correcting anaemia in the preoperative period.

Over the last decade, several observational, retrospective, and prospective studies have evaluated the role

of pre-operative therapy with iron, vitamin $B_{12}$, folate and erythropoietin [6-10] (Table 5). The timing of administration ranged from 1 day to 4-6 weeks pre-operatively. In our cohort, iron, and vitamin B12 were administered within 48-h of surgery. Although it is likely that a long lag time from supplemental therapy to surgery would reduce need for transfusion in the peri-operative period, two studies, did not demonstrated a reduction in transfusion requirements. In an observation study by Klein et al. [7], treatment with iron at a median (IQR) of 33 (15-53) days prior to surgery was not associated with a reduction in the proportion of patients needing transfusion ($p=0.127$). In another retrospective study by Quarterman et al (8), administration of iron 4-6 weeks prior surgery was not associated with a reduction in the median units of transfusion required in the peri-operative period ($p=0.24$). On the other hand, 3 studies [5,9,10] showed a beneficial effect on transfusion despite iron and/or erythropoietin and vitamin $B_{12}$ and folate being given within 7 days of surgery. The study by Jafari et al. [8] showed a significant reduction ($p<0.001$) in the requirement for transfusion (Table 5). Shokri et al. [9] showed a significant ($p<0.001$) reduction in the proportion of patients requiring transfusion. In the largest randomized controlled trial done on this subject [5], a significant reduction in need for transfusion was demonstrated.

Table 6 summarizes the key differences between the largest randomized trial on supplemental iron with the current study. Patients in our study were slightly younger, had a lower BMI and lower proportion of females and less smoking and alcohol use when compared to the Lancet study [5]. A larger proportion of patients in the current study had prior myocardial infarction. The EuroSCORE II was much lower in our cohort suggesting that our patients had low risk. The pre-operative haemoglobin was lower in the current study when compared to the Lancet study [5], while pre-operative platelet count and creatinine were similar.

The number of RBCs that were required was slightly higher in the Lancet study. In the Lancet study (5), in the treatment group, the mean (SD) units transfused in the first 90 days was significantly lower ($p=0.018$) at 1.7 (3.2) units, while in the control group it was 2.3 (3.3). In our study, 1.38 (1.11) units were transfused in the treatment group and 1.46 (1.17) in the control group ($p=0.69$). The difference between the two studies is likely to be the power of study, with the current study probably underpowered to detect a significant difference.

The lower transfusion requirement in our cohort when compared with the Lancet cohort could be attributed to younger population, lower EuroSCORE-II, less co-morbidities, and a lower proportion of females. The two studies also differ from the fact that patients in the Lancet study additionally received erythropoietin. The timing of administration of these agents were within 7 days in both groups however in our study it was within 48 hours. Our cohort was less heterogeneous with the inclusion of only patients who underwent CABG graft surgery on bypass while the Lancet study had a more heterogeneous group of patients who underwent CABG bypass graft surgery and valvular surgeries on bypass as well as off bypass.

Table 5. Summary of studies on pre-operative iron

| Study | Type | Intervention, timing | Outcome | Rx (n) | Control (n) | Outcome | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Rx | Control | |
| Current study, India 2022 | Non-randomized prospective study | 20 mg/kg of ferric carboxymaltose and 1 mg of subcutaneous vitamin B12 within 48 h of surgery | Mean (SD) units transfused | 45 | 159 | 1.38 (1.11) | 1.46 (1.17) | 0.69 |
| Jafari S et al, Tehran 2022 (9) | RCT | Iron sucrose 200 mg Erythropoietin 100 IU/Kg, 1-2 days prior to surgery | Mean (SD) units transfused | 57 | 57 | 1.53 (1.04) | 2.56 (1.35) | <0.001 |
| Klein AA et al, UK 2020 (7) | Observational | Iron isomaltoside or ferric carboxymaltose 20 mg/kg at median (IQR) of 33 days (15-53) | Proportion needing transfusion | 64 | 72 | 31 (56%) | 28 (42%) | 0.127 |
| Shokri H et al, Egypt 2022 (10) | Randomized trial | Ferric carboxymaltose 1000 mg single dose, 7 days prior to surgery | Proportion needing transfusion post-op | 40 | 40 | 5 (12.5%) | 22 (55%) | <0.001 |
| Quarterman C et al, UK 2021 (8) | Retrospective review | Iron isomaltoside 1000 mg, 4 to 6 weeks prior to surgery | Median (IQR) units transfused | 190 | 581 | 2 (1-3) | 2 (1-4) | 0.24 |
| Spahn DR et al, Switzerland 2019 (5) | RCT | 20 mg/kg ferric carboxymaltose, 40 000 U erythropoietin alpha s/c, 1 mg s/c vitamin B12, 5 mg oral folic acid on the day before surgery | Mean (SD) units transfused in the first 90 days | 243 | 241 | 1.7 (3.2) | 2.3 (3.3) | 0.018 |

RCT randomized controlled trial; SD standard deviation; IQR interquartile range; Rx treatment group; s/c subcutaneously

Table 6. Comparison of the current study with the Lancet study [5]

| Variable | Lancet study | | Current study | |
|---|---|---|---|---|
| | Cases n=243 | Controls n=241 | Cases n=45 | Controls n=159 |
| **Demographic data** | | | | |
| Age | 69 (11) | 67 (12) | 60.5 (8.4) | 61.0 (7.9) |
| Females, (%) | 85 (35%) | 82 (34%) | 12 (27%) | 31 (19%) |
| Height, (cm) | 168 (9) | 169 (10) | 162.7 (8.7) | 161.7 (8.8) |
| Weight, (kg) | 76 (15) | 77 (16) | 63.2 (10.6) | 63.3 (10.6) |
| BMI | 27.1 (4.8) | 26.9 (5.0) | 24.5 (3.4) | 24.2 (3.3) |
| History of MI, (%) | 66 (28%) | 63 (26%) | 16 (36%) | 51 (32%) |
| **Habits** | | | | |
| Alcohol use, (%) | 53 (22%) | 49 (20%) | 6 (13%) | 23 (11%) |
| Smoker, (%) | 126 (52%) | 131 (54%) | 11 (25%) | 49 (31%) |
| Tobacco chewer, (%) | NA | NA | 7 (16%) | 14 (9%) |
| **Scoring** | | | | |
| EUROSCORE II | 4.5 (5.3) | 4.2 (4.8) | 0.94 (0.43) | 0.93 (0.76) |
| **Hemodynamic variables** | | | | |
| Heart rate, per min | NA | NA | 75.3 (11.5) | 74.4 (11.3) |
| SBP, mmHg | 131 (22) | 130 (20) | 134 (15) | 135 (16) |
| DBP, mm Hg | 72 (12) | 70 (12) | 79.4 (8.5) | 80.1 (8.8) |
| **Laboratory variables** | | | | |
| Pre-op Hb, (gm/dl) | 12.8 (1.5) | 12.9 (1.5) | 11.8 (1.2) | 11.7 (1.2) |
| Platelet count, x $10^5$ | 2.4 (73000) | 2.27 (66000) | 2.32 (78073) | 2.81 (93474) |
| Creatinine, (mg/dl) | 1.01 (0.28) | 1.01 (0.29) | 1.04 (0.45) | 1.13 (0.94) |
| **Transfusion details** | | | | |
| No. of RBC transfused | 1.7 (3.2) | 2.3 (3.3) | 1.38 (1.11) | 1.46 (1.17) |
| No. of FFP transfused | 0.1 (1.1) | 0.2 (1.7) | 0.49 (1.12) | 0.44 (0.87) |
| No. Platelets transfused | 0.3 (1.1) | 0.3 (1.2) | 0.58 (1.34) | 0.91 (1.46) |

All values are mean (standard deviation) unless specified; Hb haemoglobin; NA not available; No. number; BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, MI myocardial infarction; RBC red blood cell, FFP fresh frozen plasma.

The study must be interpreted in the light of the following limitations. First and foremost, the COVID-19 pandemic resulted in lockdown and severe economic consequences because of which patient load decreased significantly. This resulted in the inability to recruit more patients. There was a delay in procurement of the study drug which also restricted the number of patients who could be recruited during the period of the study. This study was initially planned as a randomized trial. However, there was much reluctance among surgeons on the probable adverse effects of the intravenous administration of iron pre-operatively, particularly in patients with triple vessel disease and those with a high degree of occlusion. This was probably due to limited prior use of intravenous iron in the pre-operative period in this clinical setting. This resulted in the inability to follow the randomization protocol and allocation concealment due to the uncertainty if permission would be given to administer

iron after recruitment. In view of this, the study design was changed to a cohort, non-randomized study. This limits the ability to ensure that known and unknown factors were balanced in both the treatment and control arms. However, despite this, it was interesting to note that the treatment and control arms had similar baseline characteristics as well as EuroSCORE-II.

## CONCLUSIONS

In this non-randomized study of patients with anaemia and undergoing CABG using CPB, preoperative administration of iron and vitamin $B_{12}$ did not reduce transfusion requirements in the perioperative period. Female gender, higher EuroSCORE-II and longer cross-clamp time were independent risk factor for the need for 2 or more RBC transfusions in the perioperative period. Larger studies may provide definitive answers for the role of preoperative supplementation of iron and vitamin $B_{12}$.

## Statements and Declarations

### Conflict of interest statement

There was no conflict of interest for all the authors listed in this submission.

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